	elements such as relevance]	
Metric 11. Number of exposure groups and spacing of exposure levels Were the number of exposure groups and spacing of exposure levels justified by study authors (e.g., based on range-finding studies) and adequate to address the purpose of the study? Did the range of concentrations/doses tested allow for identification of endpoint values (i.e., LOAEC and NOAEC, LC_{50}, or EC_{50}, depending upon duration of study)?		
High (score = 1)	The number of exposure groups and spacing of exposure levels were justified by study authors, adequate to address the purpose of the study (e.g., the selected doses produce a range of responses), and allowed for identification of endpoint values.	
Medium (score = 2)	There were minor limitations regarding the number of exposure groups and/or spacing of exposure levels (e.g., unclear if lowest concentration was low enough), but the number of exposure groups and spacing of exposure levels were adequate to show results relevant to the outcome of interest (e.g., observation of a concentration-response relationship) and the concerns are unlikely to have a substantial impact on results.	
Low (score = 3)	There were deficiencies regarding the number of exposure groups and/or spacing of exposure levels (e.g., narrow spacing between exposure levels with similar responses across groups), which may include the omission of some important details (e.g., not all exposure levels are specified), and these are likely to have a substantial impact on results.	
Unacceptable (score = 4)	The number of exposure groups and spacing of exposure levels were not conducive to the purpose of the study (e.g., the range of concentrations tested was either too high or too low to observe a concentration-response relationship, a LOAEC, NOAEC, LC_{50}, or EC_{50} could not be identified) **OR** no information is provided on the number of exposure groups and spacing of exposure levels. These are serious flaws that make the study unusable.	
Not rated/applicable[a]		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 12. Testing at or below solubility limit Were exposure concentrations at or below the limit of water solubility (or dispersibility limit if applicable)? If a solvent was used, was the solvent concentration appropriate (i.e., no effects on biological responses were observed in the solvent control and no interactions were expected between the solvent and test substance)?		
High (score = 1)	Exposure concentrations were at or below the water solubility limit (or dispersibility limit if applicable). The solvent concentration was appropriate.	
Medium (score = 2)	A subset of the exposure concentrations exceeded the water solubility limit (or dispersibility limit if applicable) but a sufficient range of exposure concentrations was tested to characterize a concentration-response relationship **AND/OR** the solvent concentration slightly exceeded an appropriate concentration or was not reported, but the biological response of the solvent control was acceptable and no interactions are expected between the solvent and test substance. These minor uncertainties or limitations are unlikely to have a substantial impact on results.	
Low (score = 3)	Reporting omissions prevented determination of whether exposure concentrations exceeded the water solubility limit (or dispersibility limit if applicable) **AND/OR** both the solvent concentration and biological response of the solvent	

	control were not reported. These deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	All exposure concentrations greatly exceeded the water solubility limit (or dispersibility limit if applicable) and the range of exposure concentrations tested was insufficient to characterize a concentration-response relationship **AND/OR** the solvent concentration exceeded an appropriate concentration and is likely to have influenced the biological response of the test organisms. These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 4. Test Organisms		
Metric 13. Test organism characteristics Were the species, strain, sex, age, size, life stage, and/or embryonic stage of the test organisms reported and appropriate for the evaluation of the specific outcome(s) of interest (e.g., routinely used for similar study types or acceptable rationale provided for selection)? Were the test organisms from a reliable source?		
High (score = 1)	The test organisms were adequately described and were obtained from a reliable source. The test organisms were appropriate for evaluation of the specific outcome(s) of interest (e.g., routinely used for similar study types or acceptable rationale provided for selection).	
Medium (score = 2)	There are minor reservations or uncertainties about the choice of test species, source of test organisms, or characteristics of test organisms (e.g., age, size, or sex not reported for fish) that are unlikely to have a substantial impact on results.	
Low (score = 3)	There were significant deficiencies or concerns regarding the choice of test species, source of test organisms, or characteristics of test organisms that are likely to have a substantial impact on study results.	
Unacceptable (score = 4)	The test organisms were not identified sufficiently or were not appropriate for the evaluation of the specific outcome(s) of interest or were not from an appropriate source (e.g., collected from a polluted field site). These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 14. Acclimatization and pretreatment conditions Were the test organisms acclimatized to test conditions? Were pretreatment conditions the same for control and exposed groups?		
High (score = 1)	The test organisms were acclimatized to test conditions and all pretreatment conditions were the same for control and exposed populations, such that the only difference was exposure to test substance.	
Medium (score = 2)	Some acclimatization and/or pretreatment conditions differed between control and exposed populations, but the differences are unlikely to have a substantial impact on results or there are minor uncertainties or limitations in the details provided.	
Low (score = 3)	The study did not report whether test organisms were acclimatized and/or whether pretreatment conditions were the same for control and exposed	

	groups, and this is likely to have a substantial impact on results.	
Unacceptable (score = 4)	There were serious differences in acclimatization and/or pretreatment conditions between control and exposed groups **OR** organisms were previously exposed to the test substance or other unintended stressors. These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 15. Number of organisms and replicates per group Were the numbers of test organisms and replicates sufficient to characterize toxicological effects?		
High (score = 1)	The numbers of test organisms and replicates were reported and sufficient to characterize toxicological effects.	
Medium (score = 2)	The numbers of test organisms and replicates were sufficient to characterize toxicological effects, but minor uncertainties or limitations were identified regarding the number of test organisms and/or replicates that are unlikely to have a substantial impact on results.	
Low (score = 3)	The number of test organisms and/or replicates was not reported and this is likely to have a substantial impact on results.	
Unacceptable (score = 4)	The number of test organisms and/or replicates was insufficient to characterize toxicological effects and/or provided insufficient power for statistical analysis (e.g., 1-2 organisms/group). These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 16. Adequacy of test conditions Were organism housing, environmental conditions (e.g., temperature, pH, dissolved oxygen, hardness, and salinity), food, water, and nutrients conducive to maintenance of health, both before and during exposure? Was the biomass loading of the organisms in the test system appropriate?		
High (score = 1)	Organism housing, environmental conditions, food, water, and nutrients were conducive to maintenance of health and biomass loading was appropriate.	
Medium (score = 2)	Minor uncertainties or limitations were identified regarding organism housing, environmental conditions, food, water, nutrients, and/or biomass loading, but these are not likely to have a substantial impact on results.	
Low (score = 3)	Reporting of housing and/or environmental conditions and/or food, water, and nutrients and/or biomass loading was limited or unclear, and the omitted details are likely to have a substantial impact on results.	
Unacceptable (score = 4)	Organism housing and/or environmental conditions and/or food, water, and nutrients and/or biomass loading were not conducive to maintenance of health (e.g., overt signs of handling stress are evident). These are serious flaws that make the study unusable.	
Not rated/applicable[a]		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Domain 5. Outcome Assessment		
Metric 17. Outcome assessment methodology Did the outcome assessment methodology address or report the intended outcome(s) of interest? Was the outcome assessment methodology (including endpoints assessed and timing of endpoint assessment) sensitive for the outcome(s) of interest (e.g., measured endpoints that were able to detect a true biological effect or hazard)? (Note: Outcome, as addressed in this domain, refers to biological effects measured in an ecotoxicity study; e.g., reproductive toxicity.)		
High (score = 1)	The outcome assessment methodology addressed or reported the intended outcome(s) of interest and was sensitive for the outcomes(s) of interest.	
Medium (score = 2)	The outcome assessment methodology partially addressed or reported the intended outcomes(s) of interest (e.g., total number of offspring per group reported in the absence of data on fecundity per individual), but minor uncertainties or limitations are unlikely to have a substantial impact on results.	
Low (score = 3)	Significant deficiencies in the reported outcome assessment methodology were identified **OR** due to incomplete reporting, it was unclear whether methods were sensitive for the outcome of interest. This is likely to have a substantial impact on results.	
Unacceptable (score = 4)	The outcome assessment methodology was not reported **OR** the reported outcome assessment methodology was not sensitive for the outcome(s) of interest (e.g., in the assessment of reproduction in a chronic daphnid test, offspring were not counted and removed until the end of the test, rather than daily). These are serious flaws that make the study unusable.	
Not rated/applicable[a]		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 18. Consistency of outcome assessment Was the outcome assessment carried out consistently (i.e., using the same protocol) across study groups (e.g., assessment at the same time after initial exposure in all study groups)?		
High (score = 1)	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups (e.g., at the same time after initial exposure) using the same protocol in all study groups.	
Medium (score = 2)	There were minor differences in the timing of outcome assessment across study groups, or incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have substantial impact on results.	
Low (score = 3)	Details regarding the execution of the study protocol for outcome assessment (e.g., timing of assessment across groups) were not reported, and these deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups **OR** outcome assessments were not adequately reported for meaningful interpretation of results. These are serious flaws that make the study unusable.	
Not rated/applicable[a]		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any*	

	additional comments that may highlight study strengths or important elements such as relevance]	
Domain 6. Confounding/Variable Control		
Metric 19. Confounding variables in test design and procedures Were all variables consistent across experimental groups or appropriately controlled for in the analysis, including, but not limited to, size and age of test organisms, environmental conditions (e.g., temperature, pH, and dissolved oxygen), and protective or toxic factors that could mask or enhance effects?		
High (score = 1)	There were no reported differences among the study groups in environmental conditions or other factors that could influence the outcome assessment.	
Medium (score = 2)	The study reported minor differences among the study groups with respect to environmental conditions or other non-treatment-related factors, but these are unlikely to have a substantial impact on results.	
Low (score = 3)	The study did not provide enough information to allow a comparison of environmental conditions or other non-treatment-related factors across study groups, and the omitted information is likely to have a substantial impact on study results.	
Unacceptable (score = 4)	The study reported significant differences among the study groups with respect to environmental conditions (e.g., differences in pH unrelated to the test substance) or other non-treatment-related factors and these prevent meaningful interpretation of the results. These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 20. Outcomes unrelated to exposure Were there differences among the study groups in test organism attrition or outcomes unrelated to exposure (e.g., infection) that could influence the outcome assessment?		
High (score = 1)	Details regarding test organism attrition and outcomes unrelated to exposure (e.g., infection) were reported for each study group and there were no differences among groups that could influence the outcome assessment.	
Medium (score = 2)	Authors reported that one or more study groups experienced disproportionate test organism attrition or outcomes unrelated to exposure (e.g., infection), but data from the remaining exposure groups were valid and the low incidence of attrition is unlikely to have a substantial impact on results **OR** data on attrition and/or outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted (as indicated by study authors).	
Low (score = 3)	Data on attrition and/or outcomes unrelated to exposure were not reported for each study group, and this deficiency is likely to have a substantial impact on results.	
Unacceptable (score = 4)	One or more study groups experienced serious test organism attrition or outcomes unrelated to exposure (e.g., infection). This is a serious flaw that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 7. Data Presentation and Analysis		

Metric 21. Statistical methods Were statistical methods clearly described and appropriate for dataset(s) (e.g., parametric test for normally distributed data)?		
High (score = 1)	Statistical methods were clearly described and appropriate for dataset(s) (e.g., parametric test for normally distributed data). **OR** no statistical analyses, calculation methods, and/or data manipulation were conducted but sufficient data were provided to conduct an independent statistical analysis.	
Medium (score = 2)	Not applicable for this metric	
Low (score = 3)	Statistical analysis was not described clearly, and this deficiency is likely to have a substantial impact on results.	
Unacceptable score = 4)	Statistical methods used were not appropriate (e.g., parametric test for non-normally distributed data) **OR** statistical analysis was not conducted **AND** data enabling an independent statistical analysis were not provided. These are serious flaws that make the study unusable.	
Not rated/applicable[a]		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 22. Reporting of data Were the data for all outcomes presented? Were data reported for each treatment and control group? Were reported data sufficient to determine values for the endpoint(s) of interest (e.g., LOEC, NOEC, LC_{50}, and EC_{50})?		
High (score = 1)	Data for exposure-related findings were presented for each treatment and control group and were adequate to determine values for the endpoint(s) of interest. Negative findings were reported qualitatively or quantitatively.	
Medium (score = 2)	Data for exposure-related findings were reported for most, but not all, outcomes by study group and/or data were not reported for outcomes with negative findings, but these minor uncertainties or limitations are unlikely to have a substantial impact on results.	
Low (score = 3)	Data for exposure-related findings were not shown for each study group, but results were described in the text and/or data were only reported for some outcomes. These deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	Data presentation was inadequate (e.g., the report does not differentiate among findings in multiple treatment groups) **OR** major inconsistencies were present in reporting of results. These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 23. Explanation of unexpected outcomes Did the author provide a suitable explanation for unexpected outcomes (including excessive within-study variability)?		
High (score = 1)	There were no unexpected outcomes, or unexpected outcomes were satisfactorily explained.	
Medium	Minor uncertainties or limitations were identified in how the study	

(score = 2)	characterized unexpected outcomes, including within-study variability and/or variation from historical measures, but those are not likely to have a substantial impact on results.	
Low (score = 3)	The study did not report any measures of variability (e.g., SE, SD, confidence intervals) and/or insufficient information was provided to determine if excessive variability or unexpected outcomes occurred. This is likely to have a substantial impact on results.	
Unacceptable (score = 4)	The occurrence of unexpected outcomes, including, but not limited to, within-study variability and/or variation from historical measures, are considered serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 8. Other (Apply as Needed)		
Metric		
High (score = 1)		
Medium (score = 2)		
Low (score = 3)		
Unacceptable (score = 4)		
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Note:
[a]These metrics should be scored as *Not rated/applicable* if the study cited a secondary literature source for the description of testing methodology; if the study is not classified as unacceptable in the initial review, the secondary source will be reviewed during a subsequent evaluation step and the metric will be rated at that time.

F.6 References

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APPENDIX G: DATA QUALITY CRITERIA FOR STUDIES ON ANIMAL AND *IN VITRO* TOXICITY

G.1 Types of Data Sources

The data quality will be evaluated for a variety of animal and *in vitro* toxicity studies. Table G-1 provides examples of types of studies falling into these two broad categories. Since the availability of information varies considerably on different chemicals, it is anticipated that some study types will not be available while others may be identified beyond those listed in Table G-1.

Table G-1. Types of Animal and *In Vitro* Toxicity Data

Data Category	Type of Data Sources
Animal Toxicity	Oral, dermal, and inhalation routes: lethality, irritation, sensitization, reproduction, fertility, developmental, neurotoxicity, carcinogenicity, systemic toxicity, metabolism, pharmacokinetics, absorption, immunotoxicity, genotoxicity, mutagenicity, endocrine disruption
In Vitro Toxicity Studies	Irritation, corrosion, sensitization, genotoxicity, dermal absorption, phototoxicity, ligand binding, steroidogenesis, developmental, organ toxicity, mechanisms, high throughput, immunotoxicity

Mechanistic evidence is highly heterogeneous and may come from human, animal or *in vitro* toxicity studies. Mechanistic evidence may provide support for biological plausibility and help explain differences in tissue sensitivity, species, gender, life-stage or other factors (U.S. EPA, 2006). Although highly preferred, the availability of a fully elucidated mode of action (MOA) or adverse outcome pathway (AOP) is not required to conduct the human health hazard assessment for a given chemical.

EPA/OPPT plans to prioritize the evaluation of mechanistic evidence instead of evaluating all of the identified evidence upfront. This approach has the advantage of conducting a focused review of those mechanistic studies that are most relevant to the hazards under evaluation. The prioritization approach is generally initiated during the data screening step. For example, many of the human health PECOs for the first ten TSCA risk evaluation excluded mechanistic evidence during full text screening. Excluding the mechanistic evidence during full text screening does not mean that the data cannot be accessed later. The assessor can eventually mine the database of mechanistic references when specific questions or hypotheses arise related to the chemical's MOA/AOP.

Moreover, EPA/OPPT anticipates that some chemicals undergoing TSCA risk evaluations may have physiologically based pharmacokinetic (PBPK) models that could be used for predicting internal dose at a target site as well as interspecies, intraspecies, route-to-route extrapolations or other types of extrapolations. These models should be carefully evaluated to determine if they can be used for risk assessment purposes. Although EPA/OPPT is not including an evaluation strategy for PBPK models in this document, when necessary, it plans to document the model evaluation process based on the list of considerations described in U.S. EPA (2006)

and IPCS (2010). EPA/OPPT plans to use the evaluation strategies for animal and *in vitro* toxicity data to assess the quality of mechanistic and pharmacokinetic data supporting the model. EPA/OPPT may tailor the criteria to capture the inherent characteristics of particular studies that are not captured in the current criteria (e.g., optimization of criteria to evaluate the quality of new approach methodologies or NAMs).

G.2 Data Quality Evaluation Domains

The methods for evaluation of study quality were developed after review of selected references describing existing study quality and risk of bias evaluation tools for toxicity studies (EC, 2018; Cooper et al., 2016; Lynch et al., 2016; Moermond et al., 2016b; Samuel et al., 2016; NTP, 2015a; Hooijmans et al., 2014; Koustas et al., 2014; Kushman et al., 2013; Hartling et al., 2012; Hooijmans et al., 2010). These publications, coupled with professional judgment and experience, informed the identification of domains and metrics for consideration in the evaluation and scoring of study quality. Furthermore, the evaluation tool is intended to address elements of TSCA Science Standards 26(h)(1) through 26(h)(5) that EPA must address during the development process of the risk evaluations.

The data quality of animal toxicity studies and *in vitro* toxicity studies is evaluated by assessing the following seven domains: Test Substance, Test Design, Exposure Characterization, Test Organism/Test Model, Outcome Assessment, Confounding/Variable Control, and Data Presentation and Analysis. The data quality within each domain will be evaluated by assessing unique metrics that pertain to each domain. The domains are defined in Table G-2 and further information on evaluation metrics is provided in section G.3. Relevance of the studies will also be checked in continuance with relevance identification that began during the data screening process.

Table G-2. Data Evaluation Domains and Definitions

Evaluation Domain	Definition
Test Substance	Metrics in this domain evaluate whether the information provided in the study provides a reliable[a] confirmation that the test substance used in a study has the same (or sufficiently similar) identity, purity, and properties as the substance of interest.
Test Design	Metrics in this domain evaluate whether the experimental design enables the study to distinguish the effect of exposure from other factors. This domain includes metrics related to the use of control groups and randomization in allocation to ensure that the effect of exposure is isolated.
Exposure Characterization	Metrics in this domain assess the validity and reliability of methods used to measure or characterize exposure. These metrics evaluate whether exposure to the test substance was characterized using a method(s) that provides valid and reliable results, whether the exposure remained consistent over the duration of the experiment, and whether the exposure levels were appropriate to the outcome of interest.
Test Organism/Test Model	These metrics assess the appropriateness of the population or organism(s), group sizes used in the study (i.e., number of organisms and/or number of replicates per exposure group), and the organism conditions to assess the outcome of interest associated with the exposure of interest.
Outcome Assessment	Metrics in this domain assess the validity and reliability of methods, including sensitivity of methods, that are used to measure or otherwise characterize the outcome(s) of interest.

Confounding/Variable Control	Metrics in this domain assess the potential impact of factors other than exposure that may affect the risk of outcome. The metrics evaluate whether studies identify and account for factors that are related to exposure and independently related to outcome (confounding factors) and whether appropriate experimental or analytical (statistical) methods are used to control for factors unrelated to exposure that may affect the risk of outcome (variable control).
Data Presentation and Analysis	Metrics in this domain assess whether appropriate statistical methods were used and if data for all outcomes are presented.
Other	Metrics in this domain are added as needed to incorporate chemical- or study-specific evaluations.

Note:

[a] Reliability is defined as "the inherent property of a study or data, which includes the use of well-founded scientific approaches, the avoidance of bias within the study or data collection design and faithful study or data collection conduct and documentation" (ECHA, 2011a).

G.3 Data Quality Evaluation Metrics

The data quality evaluation domains are evaluated by assessing unique metrics that have been developed for animal and *in vitro* studies. Each metric is binned into a confidence level of *High*, *Medium*, *Low*, or *Unacceptable*. Each confidence level is assigned a numerical score (i.e., 1 through 4) that is used in the method of assessing the overall quality of the study.

Table G-3 lists the data evaluation domains and metrics for animal toxicity studies including metrics that inform risk of bias and types of bias, and Table G-4 lists the data evaluation domains and metrics for *in vitro* toxicity studies. Each domain has between 2 and 6 metrics; however, some metrics may not apply to all study types. A general domain for other considerations is available for metrics that are specific to a given test substance or study type.

EPA may modify the metrics used for animal toxicity and *in vitro* toxicity studies as the Agency acquires experience with the evaluation tool. Any modifications will be documented.

Table G-3. Data Evaluation Domains and Metrics for Animal Toxicity Studies

Evaluation Domain	Number of Metrics Overall	Metrics (Metric Number and Description, Type of Bias)
Test Substance	3	• Metric 1: Test Substance Identity • Metric 2: Test Substance Source • Metric 3: Test Substance Purity (*information bias[a]) (*detection bias[b])
Test Design	3	• Metric 4: Negative and Vehicle Controls (*performance bias[b]) • Metric 5: Positive Controls (*information bias[a]) • Metric 6: Randomized Allocation (*selection bias[a,b])
Exposure Characterization	6	• Metric 7: Preparation and Storage of Test Substance • Metric 8: Consistency of Exposure Administration • Metric 9: Reporting of Doses/Concentrations • Metric 10: Exposure Frequency and Duration • Metric 11: Number of Exposure Groups and Dose Spacing • Metric 12: Exposure Route and Method
Test Organism	3	• Metric 13: Test Animal Characteristics • Metric 14: Adequacy and Consistency of Animal Husbandry Conditions • Metric 15: Number per Group (*missing data bias[a])
Outcome Assessment	5	• Metric 16: Outcome Assessment Methodology (*information bias[a]) (*detection bias[b]) • Metric 17: Consistency of Outcome Assessment • Metric 18: Sampling Adequacy • Metric 19: Blinding of Assessors (*selection bias[a]) (*performance bias[b]) • Metric 20: Negative Control Response
Confounding/ Variable Control	2	• Metric 21: Confounding Variables in Test Design and Procedures (*other bias[b]) • Metric 22: Health Outcomes Unrelated to Exposure (*attrition/exclusion bias[b])
Data Presentation and Analysis	2	• Metric 23: Statistical Methods (*information bias[a]) (*other bias[b]) • Metric 24: Reporting of Data (*selective reporting bias[b])

Notes:
Items marked with an asterisk (*) are examples of items that can be used to assess internal validity/risk of bias.
[a]National Academies of Sciences, Engineering, and Medicine. 2017. *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals*. Washington, DC: The National Academies Press. doi: https://doi.org/10.17226/24758
[b]National Toxicology Program, Office of Health Assessment and Translation (OHAT). 2015. OHAT Risk of Bias Rating Tool for Human and Animal Studies. https://ntp.niehs.nih.gov/ntp/ohat/pubs/riskofbiastool_508.pdf

Table G-4. Data Evaluation Domains and Metrics for *In Vitro* Toxicity Studies

Evaluation Domain	Number of Metrics Overall	Metrics (Metric Number and Description, Type of Bias)
Test Substance	3	• Metric 1: Test Substance Identity • Metric 2: Test Substance Source • Metric 3: Test Substance Purity
Test Design	4	• Metric 4: Negative Controls [a] • Metric 5: Positive Controls [a] • Metric 6: Assay Procedures • Metric 7: Standards for Test
Exposure Characterization	6	• Metric 8: Preparation and Storage of Test Substance • Metric 9: Consistency of Exposure Administration • Metric 10: Reporting of Doses/Concentrations • Metric 11: Exposure Duration • Metric 12: Number of Exposure Groups and Dose Spacing • Metric 13: Metabolic Activation
Test Model	2	• Metric 14: Test Model • Metric 15: Number per Group
Outcome Assessment	4	• Metric 16: Outcome Assessment Methodology • Metric 17: Consistency of Outcome Assessment • Metric 18: Sampling Adequacy • Metric 19: Blinding of Assessors
Confounding/ Variable Control	2	• Metric 20: Confounding Variables in Test Design and Procedures • Metric 21: Outcomes Unrelated to Exposure
Data Presentation and Analysis	4	• Metric 22: Data Analysis • Metric 23: Data Interpretation • Metric 24: Cytotoxicity Data • Metric 25: Reporting of Data

Note:
[a] These are for the assay performance, not necessarily for the "validation" of extrapolating to a particular apical outcome (i.e., assay performance vs assay validation).

G.4 Scoring Method and Determination of Overall Data Quality Level

Appendix A provides information about the evaluation method that will be applied across the various data/information sources being assessed to support TSCA risk evaluations. This section provides details about the scoring system that will be applied to animal and *in vitro* toxicity studies, including the weighting factors assigned to each metric score of each domain.

Some metrics will be given greater weights than others, if they are regarded as key or critical metrics. Thus, EPA will use a weighting approach to reflect that some metrics are more important than others when assessing the overall quality of the data.

G.4.1 Weighting Factors

Each metric was assigned a weighting factor of 1 or 2, with the higher weighting factor (2) given to metrics deemed critical for the evaluation. The critical metrics were identified based on professional judgment in conjunction with consideration of the factors that are most frequently included in other study quality/risk of bias tools for animal toxicity studies [reviewed by Lynch et al. (2016); Samuel et al. (2016)]. In selecting critical metrics, EPA recognized that the relevance of an individual study to the risk analysis for a given substance is determined by its ability to inform hazard identification and/or dose-response assessment. Thus, the critical metrics are those that determine how well a study answers these key questions:

- Is a change in health outcome demonstrated in the study?
- Is the observed change more likely than not attributable to the substance exposure?
- At what substance dose(s) does the change occur?

EPA/OPPT assigned a weighting factor of 2 to each metric considered critical to answering these questions. Remaining metrics were assigned a weighting factor of 1. Tables G-5 and G-6 identify the critical metrics (i.e., those assigned a weighting factor of 2) for animal toxicity and *in vitro* toxicity studies, respectively, and provides a rationale for selection of each metric. Tables G-7 and G-8 identify the weighting factors assigned to each metric for animal toxicity and *in vitro* toxicity studies, respectively.

Table G-5. Animal Toxicity Metrics with Greater Importance in the Evaluation and Rationale for Selection

Domain	Critical Metrics with Weighting Factor of 2 (Metric Number) [a]	Rationale
Test substance	Test substance identity (Metric 1)	The test substance must be identified and characterized definitively to ensure that the study is relevant to the substance of interest.
Test design	Negative and vehicle controls (Metric 4)	A concurrent negative control and vehicle control (when indicated) are required to ensure that any observed effects are attributable to substance exposure. Note that more than one negative control may be necessary in some studies.
Exposure characterization	Reporting of doses/concentrations (Metric 9)	Dose levels must be defined without ambiguity to allow for determination of the dose-response relationship and to enable valid comparisons across studies.
Test organisms	Test animal characteristics (Metric 13)	The test animal characteristics must be reported to enable assessment of a) whether they are suitable for the endpoint of interest; b) whether there are species, strain, sex, or age/lifestage differences within or between different studies; and c) to enable consideration of approaches for extrapolation to humans.
Outcome assessment	Outcome assessment methodology (Metric 16)	The methods used for outcome assessment must be fully described, valid, and sensitive to ensure that effects are detected, that observed effects are true, and to enable valid comparisons across studies.
Confounding/ variable control	Confounding variables in test design and procedures (Metric 21)	Control for confounding variables in test design and procedures is necessary to ensure that any observed effects are attributable to substance exposure and not to other factors.
Data presentation and analysis	Reporting of data (Metric 24)	Detailed results are necessary to determine if the study authors' conclusions are valid and to enable dose-response modeling.

Note:
[a]A weighting factor of 1 is assigned for the remaining metrics.

Table G-6. *In Vitro* Toxicity Metrics with Greater Importance in the Evaluation and Rationale for Selection

Domain	Critical Metrics with Weighting Factor of 2 (Metric Number) [a]	Rationale
Test Substance	Test Substance Identity (Metric 1)	The test substance must be identified and characterized definitively to ensure that the study is relevant to the substance of interest.
Test Design	Negative and Vehicle Controls (Metric 4)	A concurrent negative control and vehicle control (when indicated) are required for comparison of results between exposed and unexposed models to allow determination of treatment-related effects.
	Positive Controls (Metric 5)	A concurrent positive control or proficiency control (when applicable) is required to determine if the chemical of interest produces the intended outcome for the study type.
Exposure Characterization	Reporting of concentrations (Metric 10)	Dose levels must be defined without ambiguity to allow for determination of an accurate dose-response relationship or and to ensure valid comparisons across studies.
	Exposure duration (Metric 11)	The exposure duration during the study must be defined to accurately assess potential risk.
Test Model	Test Model (Metric 14)	The identity of the test model must be reported and suitable for the evaluation of outcome(s) of interest.
Outcome Assessment	Outcome assessment methodology (Metric 16)	The methods used for outcome assessment must be fully described, valid, and sensitive to ensure that effects are detected and that observed effects are true.
	Sampling adequacy (Metric 18)	The number of samples evaluated must be sufficient to allow data interpretation and analysis.
Confounding/Variable Control	Confounding variables in test design and procedures (Metric 20)	Control for confounding variables in test design and procedures are necessary to ensure that any observed effects are attributable to substance exposure and not to other factors.
Data Presentation and Analysis	Data interpretation (Metric 23)	The criteria for scoring and/or evaluation criteria are necessary so that the correct categorization (e.g., positive, negative, equivocal) can be determined for the chemical of interest.
	Reporting of data (Metric 25)	Detailed results are necessary to determine if the study authors' conclusions are valid and to enable dose-response modeling.

Note:
[a] A weighting factor of 1 is assigned for the remaining metrics.

G.4.2 Calculation of Overall Study Score

A confidence level (1, 2, or 3 for *High, Medium*, or *Low* confidence, respectively) is assigned for each relevant metric within each domain. To determine the overall study score, the first step is to multiply the score for each metric (1, 2, or 3 for *High, Medium*, or *Low* confidence, respectively) by the appropriate weighting factor (as shown in Tables G-7 and G-8 for animal toxicity and *in vitro* studies, respectively) to obtain a weighted metric score. The weighted metric scores are then summed and divided by the sum of the weighting factors (for all metrics that are scored) to obtain an overall study score between 1 and 3. The equation for calculating the overall score is shown below:

$$\textit{Overall Score (range of 1 to 3)} = \sum (\textit{Metric Score} \times \textit{Weighting Factor}) / \sum (\textit{Weighting Factors})$$

Some metrics may not be applicable to all study types. These metrics will not be included in the nominator or denominator of the equation above. The overall score will be calculated using only those metrics that receive a numerical score. Scoring examples for animal toxicity and *in vitro* toxicity studies are in tables G-9 through G-12.

Studies with any single metric scored as unacceptable (score = 4) will be automatically assigned an overall quality score of 4 (*Unacceptable*). An unacceptable score means that serious flaws are noted in the domain metric that consequently make the data unusable. If a metric is not applicable for a study type, the serious flaws would not be applicable for that metric and would not receive a score. EPA/OPPT plans to use data with an overall quality level of High, Medium, or Low confidence to quantitatively or qualitatively support the risk evaluations, but does not plan to use data rated as *Unacceptable.* An overall study score will not be calculated when a serious flaw is identified for any metric. If a publication reports more than one study or endpoint, each study and, as needed, each endpoint will be evaluated separately.

Detailed tables showing quality criteria for the metrics are provided in Tables G-13 through G-16 for animal toxicity and *in vitro* toxicity studies, including a table that summarizes the serious flaws that would make the data unacceptable for use in the environmental hazard assessment

Table G-7. Metric Weighting Factors and Range of Weighted Metric Scores for Animal Toxicity Studies

Domain Number/ Description	Metric Number/Description	Range of Metric Scores[a]	Metric Weighting Factor	Range of Weighted Metric Scores[b]
1. Test Substance	1. Test Substance Identity	1 to 3	2	2 to 6
	2. Test Substance Source		1	1 to 3
	3. Test Substance Purity		1	1 to 3
2. Test Design	4. Negative and Vehicle Controls		2	2 to 6
	5. Positive Controls		1	1 to 3
	6. Randomized Allocation		1	1 to 3
3. Exposure Characterization	7. Preparation and Storage of Test Substance		1	1 to 3
	8. Consistency of Exposure Administration		1	1 to 3
	9. Reporting of Doses/Concentrations		2	2 to 6
	10. Exposure Frequency and Duration		1	1 to 3
	11. Number of Exposure Groups and Dose Spacing		1	1 to 3
	12. Exposure Route and Method		1	1 to 3
4. Test Organisms	13. Test Animal Characteristics		2	2 to 6
	14. Adequacy and Consistency of Animal Husbandry Conditions		1	1 to 3
	15. Number per Group		1	1 to 3
5. Outcome Assessment	16. Outcome Assessment Methodology		2	2 to 6
	17. Consistency of Outcome Assessment		1	1 to 3
	18. Sampling Adequacy		1	1 to 3
	19. Blinding of Assessors		1	1 to 3
	20. Negative Control Response		1	1 to 3
6. Confounding/ Variable Control	21. Confounding Variables in Test Design and Procedures		2	2 to 6
	22. Health Outcomes Unrelated to Exposure		1	1 to 3
7. Data Presentation and Analysis	23. Statistical Methods		1	1 to 3
	24. Reporting of Data		2	2 to 6
	Sum (if all metrics scored)[c]		31	31 to 93
Range of Overall Scores, where Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor High: ≥1 and <1.7 | Medium: ≥1.7 and <2.3 | Low: ≥2.3 and ≤3				31/31=1; 93/31=3 Range of overall score = 1 to 3[d]

Notes:

[a] For the purposes of calculating an overall study score, the range of possible metric scores is 1 to 3 for each metric, corresponding to high and low confidence. No calculations will be conducted if a study receives an "unacceptable" rating (score of "4") for any metric.

[b] The range of weighted scores for each metric is calculated by multiplying the range of metric scores (1 to 3) by the weighting factor for that metric.

[c] The sum of weighting factors and the sum of the weighted scores will differ if some metrics are not scored (not applicable).

[d] The range of possible overall scores is 1 to 3. If a study receives a score of 1 for every metric, then the overall

study score will be 1. If a study receives a score of 3 for every metric, then the overall study score will be 3.

Table G-8. Metric Weighting Factors and Range of Weighted Metric Scores for *In Vitro* Toxicity Studies

Domain Number/ Description	Metric Number/Description	Range of Metric Scores[a]	Metric Weighting Factor	Range of Weighted Metric Scores[b]
1. Test Substance	1. Test Substance Identity	1 to 3	2	2 to 6
	2. Test Substance Source		1	1 to 3
	3. Test Substance Purity		1	1 to 3
2. Test Design	4. Negative and Vehicle Controls		2	2 to 6
	5. Positive Controls		2	2 to 6
	6. Assay Procedures		1	1 to 3
	7. Standards for Test		1	1 to 3
3. Exposure Characterization	8. Preparation and Storage of Test Substance		1	1 to 3
	9. Consistency of Exposure Administration		1	1 to 3
	10. Reporting of Concentrations		2	2 to 6
	11. Exposure Duration		2	2 to 6
	12. Number of Exposure Groups and Dose Spacing		1	1 to 3
	13. Metabolic Activation		1	1 to 3
4. Test model	14. Test Model		2	2 to 6
	15. Number per Group		1	1 to 3
5. Outcome Assessment	16. Outcome Assessment Methodology		2	2 to 6
	17. Consistency of Outcome Assessment		1	1 to 3
	18. Sampling Adequacy		2	2 to 6
	19. Blinding of Assessors		1	1 to 3
6. Confounding/ Variable Control	20. Confounding Variables in Test design and Procedures		2	2 to 6
	21. Outcomes Unrelated to Exposure		1	1 to 3
7. Data Presentation and Analysis	22. Data Analysis		1	1 to 3
	23. Data Interpretation		2	2 to 6
	24. Cytotoxicity Data		1	1 to 3
	25. Reporting of Data		2	2 to 6
	Sum (if all metrics scored)[c]		36	36 - 108
Range of Overall Scores, where Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor				36/36=1; 108/36=3
High: ≥1 and <1.7 | Medium: ≥1.7 and <2.3 | Low: ≥2.3 and ≤3				Range of overall score = 1 to 3[d]

Notes:

[a] For the purposes of calculating an overall study score, the range of possible metric scores is 1 to 3 for each metric, corresponding to high and low confidence. No calculations will be conducted if a study receives an "unacceptable" rating (score of "4") for any metric.

[b] The range of weighted scores for each metric is calculated by multiplying the range of metric scores (1 to 3) by the weighting factor for that metric.

[c] The sum of weighting factors and the sum of the weighted scores will differ if some metrics are not scored (not applicable).

[d] The range of possible overall scores is 1 to 3. If a study receives a score of 1 for every metric, then the overall

study score will be 1. If a study receives a score of 3 for every metric, then the overall study score will be 3.

Table G-9. Scoring Example for Animal Toxicity Study with all Metrics Scored

Domain	Metric	Metric Score	Metric Weighting Factor	Weighted Score
Test substance	1. Test substance identity	2	2	4
	2. Test substance source	3	1	3
	3. Test substance purity	2	1	2
Test design	4. Negative and vehicle controls	1	2	2
	5. Positive controls	2	1	2
	6. Randomized allocation	3	1	3
Exposure characterization	7. Preparation and storage of test substance	2	1	2
	8. Consistency of exposure administration	2	1	2
	9. Reporting of doses/concentrations	1	2	2
	10. Exposure frequency and duration	2	1	2
	11. Number of exposure groups and dose spacing	1	1	1
	12. Exposure route and method	1	1	1
Test organisms	13. Test animal characteristics	2	2	4
	14. Consistency of animal conditions	2	1	2
	15. Number per group	1	1	1
Outcome assessment	16. Outcome assessment methodology	2	2	4
	17. Consistency of outcome assessment	3	1	3
	18. Sampling adequacy	2	1	2
	19. Blinding of assessors	3	1	3
	20. Negative control responses	2	1	2
Confounding/variable control	21. Confounding variables in test design and procedures	2	2	4
	22. Health outcomes unrelated to exposure	2	1	2
Data presentation and analysis	23. Statistical methods	2	1	2
	24. Reporting of data	2	2	4
NR= not rated/not applicable	Sum of scores		31	59
	Overall Study Score	**1.9**	**= Medium**	

Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factors

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥2.3 and ≤3

Table G-10. Scoring Example for Animal Toxicity Study with Some Metrics Not Rated/Not Applicable

Domain	Metric	Metric Score	Metric Weighting Factor	Weighted Score
Test substance	1. Test substance identity	2	2	4
	2. Test substance source	3	1	3
	3. Test substance purity	2	1	2
Test design	4. Negative and vehicle controls	1	2	2
	5. Positive controls	NR		
	6. Randomized allocation	3	1	3
Exposure characterization	7. Preparation and storage of test substance	2	1	2
	8. Consistency of exposure administration	NR		
	9. Reporting of doses/concentrations	1	2	2
	10. Exposure frequency and duration	2	1	2
	11. Number of exposure groups and dose spacing	1	1	1
	12. Exposure route and method	1	1	1
Test organisms	13. Test animal characteristics	2	2	4
	14. Consistency of animal conditions	2	1	2
	15. Number per group	1	1	1
Outcome assessment	16. Outcome assessment methodology	2	2	4
	17. Consistency of outcome assessment	NR		
	18. Sampling adequacy	2	1	2
	19. Blinding of assessors	NR		
	20. Negative control responses	2	1	2
Confounding/variable control	21. Confounding variables in test design and procedures	2	2	4
	22. Health outcomes unrelated to exposure	2	1	2
Data presentation and analysis	23. Statistical methods	2	1	2
	24. Reporting of data	2	2	4
NR= not rated/not applicable	Sum		27	49
	Overall Study Score		**1.8 = Medium**	
Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor				

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥2.3 and ≤3

Table G-11. Scoring Example for *In Vitro* Study with all Metrics Scored

Domain	Metric	Metric Score	Metric Weighting Factor	Weighted Score
Test substance	1. Test substance identity	1	2	2
	2. Test substance source	2	1	2
	3. Test substance purity	2	1	2
Test design	4. Negative controls	1	2	2
	5. Positive controls	1	2	2
	6. Assay procedures	2	1	2
	7. Standards for test	3	1	3
Exposure characterization	8. Preparation and storage of test substance	2	1	2
	9. Consistency of exposure administration	2	1	2
	10. Reporting of concentrations	1	2	2
	11. Exposure duration	1	2	2
	12. Number of exposure groups and dose spacing	1	1	1
	13. Metabolic activation	3	1	3
Test Model	14. Test model	2	2	4
	15. Number per group	2	1	2
Outcome assessment	16. Outcome assessment methodology	3	2	6
	17. Consistency of outcome assessment	2	1	2
	18. Sampling adequacy	1	2	2
	19. Blinding of assessors	2	1	2
Confounding/variable control	20. Confounding variables in test design and procedures	3	2	6
	21. Outcomes unrelated to exposure	2	1	2
Data presentation and analysis	22. Data analysis	1	1	1
	23. Data interpretation	2	2	4
	24. Cytotoxicity data	2	1	2
	25. Reporting of data	3	2	6
NR= not rated/not applicable	Sum		36	66
	Overall Study Score		**1.8 = Medium**	

Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥2.3 and ≤3

Table G-12. Scoring Example for *In Vitro* Study with Some Metrics Not Rated/Not Applicable

Domain	Metric	Metric Score	Metric Weighting Factor	Weighted Score
Test substance	1. Test substance identity	1	2	2
	2. Test substance source	2	1	2
	3. Test substance purity	2	1	2
Test design	4. Negative controls	1	2	2
	5. Positive controls	1	2	2
	6. Assay procedures	2	1	2
	7. Standards for test	3	1	3
Exposure characterization	8. Preparation and storage of test substance	NR		
	9. Consistency of exposure administration	2	1	2
	10. Reporting of concentrations	1	2	2
	11. Exposure duration	1	2	2
	12. Number of exposure groups and dose spacing	1	1	1
	13. Metabolic activation	NR		
Test Model	14. Test model	2	2	4
	15. Number per group	3	1	3
Outcome assessment	16. Outcome assessment methodology	3	2	6
	17. Consistency of outcome assessment	2	1	2
	18. Sampling adequacy	1	2	2
	19. Blinding of assessors	NR		
Confounding/variable control	20. Confounding variables in test design and procedures	3	2	6
	21. Outcomes unrelated to exposure	2	1	2
Data presentation and analysis	22. Data analysis	1	1	1
	23. Data interpretation	2	2	4
	24. Cytotoxicity data	NR		
	25. Reporting of data	3	2	6
NR= not rated/not applicable		Sum	32	58
		Overall Study Score	**1.8 = Medium**	

Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥2.3 and ≤3

G.5 Data Quality Criteria

G.5.1 Animal Toxicity Studies

Optimization of the list of serious flaws may occur after pilot calibration exercises.

Table G-13. Serious Flaws that Would Make Animal Toxicity Studies Unacceptable

Domain	Metric	Description of Serious Flaw(s) in Data Source
Test substance	Test substance identity	The test substance identity and form (the latter if applicable) cannot be determined from the information provided (e.g., nomenclature was unclear and CASRN or structure were not reported) **OR** for mixtures, the components and ratios were not characterized.
	Test substance source	The test substance was not obtained from a manufacturer **OR** if synthesized or extracted, analytical verification of the test substance was not conducted.
	Test substance purity	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities.
Test design	Negative and vehicle controls	A concurrent negative control group was not included or reported **OR** the reported negative control group was not appropriate (e.g., age/ weight of animals differed between control and treated groups).
	Positive controls	For study types that require a concurrent positive control group: When applicable, an appropriate concurrent positive control (i.e., inducing a positive response) was not used and its omission is a serious flaw that makes the study unusable.
	Randomized allocation of animals	The study reported using a biased method to allocate animals to study groups (e.g., judgement of investigator).
Exposure characterization	Preparation and storage of test substance	Information on preparation and storage was not reported **OR** serious flaws reported with test substance preparation and/or storage conditions will have critical impacts on dose/concentration estimates and make the study unusable (e.g., instability of test substance in exposure medium was reported, or there was heterogeneous distribution of test substance in exposure matrix [e.g., aerosol deposition in exposure chamber, insufficient mixing of dietary matrix]). For inhalation studies, there was no mention of the method and equipment used to generate the test substance, or the method used is

		atypical and inappropriate.
	Consistency of exposure administration	Critical exposure details (e.g., methods for generating atmosphere in inhalation studies) were not reported **OR** reported information indicated that exposures were not administered consistently across study groups (e.g., differing particle size), resulting in serious flaws that make the study unusable.
	Reporting of doses/concentrations	The reported exposure levels could not be validated (e.g., lack of food or water intake data for dietary or water exposures in conjunction with evidence of palatability differences, lack of body weight data in conjunction with qualitative evidence for body weight differences across groups, inconsistencies in reporting, etc.). For inhalation studies, actual concentrations not reported along with animal responses (or lack of responses) that indicate exposure problems due to faulty test substance generation. Animals were exposed to an aerosol but no particle size data were reported.
	Exposure frequency and duration	The exposure frequency or duration of exposure were not reported **OR** the reported exposure frequency and duration were not suited to the study type and/or outcome(s) of interest (e.g., study length inadequate to evaluate tumorigenicity).
	Number of exposure groups and dose/concentration spacing	The number of exposure groups and spacing were not reported **OR** dose groups and spacing were not relevant for the assessment (e.g., all doses in a developmental toxicity study produced overt maternal toxicity).
	Exposure route and method	The route or method of exposure was not reported **OR** an inappropriate route or method (e.g., administration of a volatile organic compound via the diet) was used for the test substance without taking steps to correct the problem (e.g., mixing fresh diet, replacing air in static chambers). For inhalation studies, there is no description of the inhalation chamber used, or an atypical exposure method was used, such as allowing a container of test substance to evaporate in a room.
Test organisms	Test animal characteristics	The test animal species was not reported **OR** the test animal (species, strain, sex, life-stage, source) was not appropriate for the evaluation of the specific outcome(s) of interest (e.g., genetically modified animals, strain was uniquely susceptible or resistant to one or more outcome of interest).
	Adequacy and consistency of animal husbandry conditions	There were significant differences in husbandry conditions between control and exposed groups (e.g., temperature, humidity, light-dark cycle) **OR** animal husbandry conditions deviated from customary

		practices in ways likely to impact study results (e.g., injuries and stress due to cage overcrowding).
	Number of animals per group	The number of animals per study group was not reported **OR** the number of animals per study group was insufficient to characterize toxicological effects (e.g., 1-2 animals in each group).
Outcome assessment	Outcome assessment methodology	The outcome assessment methodology was not reported **OR** the reported outcome assessment methodology was not sensitive for the outcome(s) of interest (e.g., evaluation of endpoints outside the critical window of development, a systemic toxicity study that evaluated only grossly observable endpoints, such as clinical signs and mortality, etc.).
	Consistency of outcome assessment	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups **OR** outcome assessments were not adequately reported for meaningful interpretation of results.
	Sampling adequacy	Sampling was not adequate for the outcome(s) of interest (e.g., histopathology was performed on exposed groups, but not controls).
	Blinding of assessors	Information in the study report did not report whether assessors were blinded to treatment group for subjective outcomes and suggested that the assessment of subjective outcomes (e.g., functional observational battery, qualitative neurobehavioral endpoints, histopathological re-evaluations) was performed in a biased fashion (e.g., assessors of subjective outcomes were aware of study groups). This is a serious flaw that makes the study unusable.
	Negative control responses	The biological responses of the negative control groups were not reported **OR** there was unacceptable variation in biological responses between control replicates.
Confounding/ variable control	Confounding variables in test design and procedures	The study reported significant differences among the study groups with respect to initial body weight, decreased drinking water/food intake due to palatability issues (≥20% difference from control) that could lead to dehydration and/or malnourishment, or reflex bradypnea that could lead to decreased oxygenation of the blood.
	Health outcomes unrelated to exposure	One or more study groups experienced serious animal attrition or health outcomes unrelated to exposure (e.g., infection).
Data presentation and analysis	Statistical methods	Statistical methods used were not appropriate (e.g., parametric test for non-normally distributed data) **OR** statistical analysis was not conducted **AND**

		data were not provided preventing an independent statistical analysis.
	Reporting of data	Data presentation was inadequate (e.g., the report does not differentiate among findings in multiple exposure groups) **OR** major inconsistencies were present in reporting of results.

Table G-14. Data Quality Criteria for Animal Toxicity Studies

Confidence Level (Score)	Description	Selected Score
Domain 1. Test Substance		
Metric 1. Test substance identity Was the test substance identified definitively (i.e., established nomenclature, CASRN, and/or structure reported, including information on the specific form tested [particle characteristics for solid-state materials, salt or base, valence state, hydration state, isomer, radiolabel, etc.] for materials that may vary in form)? If test substance is a mixture, were mixture components and ratios characterized?		
High (score = 1)	The test substance was identified definitively and the specific form was characterized (where applicable). For mixtures, the components and ratios were characterized.	
Medium (score = 2)	The test substance and form (the latter if applicable) were identified and components and ratios of mixtures were characterized, but there were minor uncertainties (e.g., minor characterization details were omitted) that are unlikely to have a substantial impact on results.	
Low (score = 3)	The test substance and form (the latter if applicable) were identified and components and ratios of mixtures were characterized, but there were uncertainties regarding test substance identification or characterization that are likely to have a substantial impact on results.	
Unacceptable (score = 4)	The test substance identity and form (the latter if applicable) cannot be determined from the information provided (e.g., nomenclature was unclear and CASRN or structure were not reported) **OR** for mixtures, the components and ratios were not characterized. These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 2. Test substance source Was the source of the test substance reported, including manufacturer and batch/lot number for materials that may vary in composition? If synthesized or extracted, was test substance identity verified by analytical methods?		
High (score = 1)	The source of the test substance was reported, including manufacturer and batch/lot number for materials that may vary in composition, and its identity was certified by manufacturer and/or verified by analytical methods (melting point, chemical analysis, etc.).	
Medium (score = 2)	The source of the test substance and/or the analytical verification of a synthesized test substance was reported incompletely, but the omitted details are unlikely to have a substantial impact on results.	
Low (score = 3)	Omitted details on the source of the test substance and/or the analytical verification of a synthesized test substance are likely to have a substantial impact on results.	
Unacceptable (score = 4)	The test substance was not obtained from a manufacturer **OR** if synthesized or extracted, analytical verification of the test substance was not conducted. These are serious flaws that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 3. Test substance purity		

Was the purity or grade (i.e., analytical, technical) of the test substance reported and adequate to identify its toxicological effects? Were impurities identified? Were impurities present in quantities that could influence the results?		
High (score = 1)	The test substance purity and composition were such that any observed effects were highly likely to be due to the nominal test substance itself (e.g., highly pure or analytical-grade test substance or a formulation comprising primarily inert ingredients with small amount of active ingredient).	
Medium (score = 2)	Minor uncertainties or limitations were identified regarding the test substance purity and composition; however, the purity and composition were such that observed effects were more likely than not due to the nominal test substance, and any identified impurities are unlikely to have a substantial impact on results. Alternately, purity was not reported but given other information purity was not expected to be of concern.	
Low (score = 3)	Purity and/or grade of test substance were not reported or were low enough to have a substantial impact on results (i.e., observed effects may not be due to the nominal test substance).	
Unacceptable (score = 4)	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities. This is a serious flaw that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 2. Test Design		
Metric 4. Negative and vehicle controls Was an appropriate concurrent negative control group included? If a vehicle was used, was the control group exposed to the vehicle? For inhalation and gavage studies, were controls sham-exposed?		
High (score = 1)	Study authors reported using an appropriate concurrent negative control group (i.e., all conditions equal except chemical exposure). If gavage or inhalation study, a vehicle and/or sham-treated control group was included.	
Medium (score = 2)	Study authors reported using a concurrent negative control group, but all conditions were not equal to those of treated groups; however, the identified differences are considered to be minor limitations that are unlikely to have a substantial impact on results.	
Low (score = 3)	Study authors acknowledged using a concurrent negative control group, but details regarding the negative control group were not reported, and the lack of details is likely to have a substantial impact on results.	
Unacceptable (score = 4)	A concurrent negative control group was not included or reported **OR** the reported negative control group was not appropriate (e.g., age/ weight of animals differed between control and treated groups). This is a serious flaw that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 5. Positive controls Was an appropriate concurrent positive control group included if necessary based on study type (e.g., certain neurotoxicity studies)? This metric is not rated/applicable if positive control was not indicated by study type.		
High	When applicable, A concurrent positive control was used (if necessary for	

(score = 1)	the study type) and a positive response was observed.	
Medium (score = 2)	When applicable, A concurrent positive control was used, but there were minor uncertainties (e.g., minor details regarding control exposure or response were omitted) that are unlikely to have a substantial impact on results.	
Low (score = 3)	When applicable, A concurrent positive control was used, but there were deficiencies regarding the control exposure or response that are likely to have a substantial impact on results (e.g., the control response was not described).	
Unacceptable (score = 4)	When applicable, an appropriate concurrent positive control (i.e., inducing a positive response) was not used and its omission is a serious flaw that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 6. Randomized allocation of animals Did the study explicitly report randomized allocation of animals to study groups?		
High (score = 1)	The study reported that animals were randomly allocated into study groups (including the control group).	
Medium (score = 2)	The study reported methods of allocation of animals to study groups, but there were minor limitations in the allocation method (e.g., method with a nonrandom component like assignment to minimize differences in body weight across groups) that are unlikely to have a substantial impact on results.	
Low (score = 3)	The study did not report how animals were allocated to study groups, or there were deficiencies regarding the allocation method that are likely to have a substantial impact on results (e.g., allocation by animal number).	
Unacceptable (score = 4)	The study reported using a biased method to allocate animals to study groups (e.g., judgement of investigator). This is a serious flaw that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Exposure Characterization		
Metric 7. Preparation and storage of test substance Did the study characterize the test substance preparation and storage conditions (e.g., test substance stability, homogeneity, mixing temperature, stock concentration, stirring methods, centrifugation/filtration)? Were the frequency of preparation and/or storage conditions appropriate to the test substance stability? For inhalation studies, was the aerosol/vapor generation method appropriate?		
High (score = 1)	The test substance preparation and storage conditions were reported and appropriate for the test substance (e.g., test substance well-mixed in diet). For inhalation studies, the method and equipment used to generate the test substance as a gas, vapor, or aerosol were reported and appropriate.	
Medium	The test substance preparation and storage conditions were reported, but	

(score = 2)	there were only minor limitations in the test substance preparation and/or storage conditions were identified (i.e., diet was not mixed fresh daily) or omission of details that are unlikely to have a substantial impact on results. For inhalation studies, the method and equipment used to generate the test substance were incomplete or confusing but there is no reason to believe there was an impact on animal exposure.	
Low (score = 3)	Deficiencies in reporting of test substance preparation and/or storage conditions are likely to have a substantial impact on results (e.g., available information on physical-chemical properties suggested that stability and/or solubility of test substance in vehicle may be poor). For inhalation studies, there is reason to question the validity of the method used for generating the test substance.	
Unacceptable (score = 4)	Information on preparation and storage was not reported **OR** serious flaws reported with test substance preparation and/or storage conditions will have critical impacts on dose/concentration estimates and make the study unusable (e.g., instability of test substance in exposure medium was reported, or there was heterogeneous distribution of test substance in exposure matrix [e.g., aerosol deposition in exposure chamber, insufficient mixing of dietary matrix]). For inhalation studies, there was no mention of the method and equipment used to generate the test substance, or the method used is atypical and inappropriate.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 8. Consistency of exposure administration Were exposures administered consistently across study groups (e.g., same exposure frequency; same time of day; consistent gavage volumes or diet compositions in oral studies; consistent chamber designs, animals/ chamber, and comparable particle size characteristics in inhalation studies; consistent application methods and volumes in dermal studies)?		
High (score = 1)	Details of exposure administration were reported and exposures were administered consistently across study groups in a scientifically sound manner (e.g., gavage volume was not excessive).	
Medium (score = 2)	Details of exposure administration were reported, but minor limitations in administration of exposures (e.g., accidental mistakes in dosing) were identified that are unlikely to have a substantial impact on results.	
Low (score = 3)	Details of exposure administration were reported, but deficiencies in administration of exposures (e.g., exposed at different times of day) are likely to have a substantial impact on results.	
Unacceptable (score = 4)	Critical exposure details (e.g., methods for generating atmosphere in inhalation studies) were not reported **OR** reported information indicated that exposures were not administered consistently across study groups (e.g., differing particle size), resulting in serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 9. Reporting of doses/concentrations Were doses/concentrations reported without ambiguity (e.g., point estimate in addition to a range)? In oral studies, if doses were not reported, was information reported that enabled dose estimation (e.g., test animal		

dietary intake and body weight monitoring data in dietary studies)? In inhalation studies, was test substance vapor/aerosol concentration measured analytically along with nominal and target concentrations?		
High (score = 1)	For oral and dermal studies, administered doses/concentrations, or the information to calculate them, were reported without ambiguity. For inhalation studies, several specific considerations apply: Analytical, nominal and target chamber concentrations were all reported, with high confidence in the accuracy of the actual concentrations; the range of concentrations within a treatment group did not deviate widely (range should be within ±10% for gases and vapors and within ±20% for liquid and solid aerosols). The analytical method (HPLC, GC, IR spectrophotometry, etc.) used to measure chamber test substance and vehicle concentration was reported and appropriate. Actual chamber measurements using gravimetric filters are acceptable when testing dry aerosols and non-volatile liquid aerosols. The particle size distribution data, mass median aerodynamic diameter (MMAD), and geometric standard deviation were reported for all exposed groups (including vehicle controls, when used).	
Medium (score = 2)	For oral and dermal studies, minor uncertainties in reporting of administered doses/concentrations occurred (e.g., dietary or air concentrations were not measured analytically) but are unlikely to have a substantial impact on results. For inhalation studies, several specific considerations apply: With gases only, actual concentrations were not reported but there is high confidence that the animals were exposed at approximately the reported target concentrations. [There is no comparable medium result for aerosols and vapors if analytical concentrations are not reported.] For inhalation studies (gas, vapor, aerosol), the analytical method used was less than ideal or subject to interference but nevertheless yielded fairly reliable measurements of chamber concentrations. Particle size distribution data were not reported, but mass median aerodynamic diameter (MMAD), and geometric standard deviation values were reported for all exposed groups (including vehicle controls, when used).	
Low (score = 3)	For oral and dermal studies, deficiencies in reporting of administered doses/concentrations occurred (e.g., no information on animal body weight or intake were provided) that are likely to have a substantial impact on results. For inhalation studies, several considerations apply: Using aerosols and vapors, a score of low is indicated if actual concentrations are not reported or the analytical method used, such as sampling tubes (e.g., Draeger tubes) provided imprecise measurements. An MMAD is reported but no geometric standard deviation or particle size distribution data were reported.	
Unacceptable (score = 4)	The reported exposure levels could not be validated (e.g., lack of food or water intake data for dietary or water exposures in conjunction with evidence of palatability differences, lack of body weight data in conjunction	

	with qualitative evidence for body weight differences across groups, inconsistencies in reporting, etc.). This is a serious flaw that makes the study unusable. For inhalation studies, actual concentrations were not reported along with animal responses (or lack of responses) that indicate exposure problems due to faulty test substance generation. Animals were exposed to an aerosol but no MMAD or particle size data were reported.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 10. Exposure frequency and duration Were the exposure frequency (hours/day and days/week) and duration of exposure reported and appropriate for this study type and/or outcome(s) of interest?		
High (score = 1)	The exposure frequency and duration of exposure were reported and appropriate for this study type and/or outcome(s) of interest (e.g., inhalation exposure 6 hours/day, gavage 5 days/week, 2-year duration for cancer bioassays).	
Medium (score = 2)	Minor limitations in exposure frequency and duration of exposure were identified (e.g., inhalation exposure of 4 hours/day instead of 6 hours/day in a repeated exposure study), but are unlikely to have a substantial impact on results.	
Low (score = 3)	The duration of exposure and/or exposure frequency differed significantly from typical study designs (e.g., gavage 1 day/week) and these deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	The exposure frequency or duration of exposure were not reported **OR** the reported exposure frequency and duration were not suited to the study type and/or outcome(s) of interest (e.g., study length inadequate to evaluate tumorigenicity). These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 11. Number of exposure groups and dose/concentration spacing Were the number of exposure groups and dose/concentration spacing justified by study authors (e.g., based on range-finding studies) and adequate to address the purpose of the study (e.g., to evaluate dose-response relationships, identify points of departure, inform MOA/AOP, etc.)?		
High (score = 1)	The number of exposure groups and dose/concentration spacing were justified by study authors and considered adequate to address the purpose of the study (e.g., the selected doses produce a range of responses).	
Medium (score = 2)	There were minor limitations regarding the number of exposure groups and/or dose/concentration spacing (e.g., unclear if lowest dose was low enough or the highest dose was high enough), but the number of exposure groups and spacing of exposure levels were adequate to show results relevant to the outcome of interest (e.g., observation of a dose-response relationship) and the concerns are unlikely to have a substantial impact on results.	

Low (score = 3)	There were deficiencies regarding the number of exposure groups and/or dose/concentration spacing (e.g., narrow spacing between doses with similar responses across groups), and these are likely to have a substantial impact on results.	
Unacceptable (score = 4)	The number of exposure groups and spacing were not reported **OR** dose groups and spacing were not relevant for the assessment (e.g., all doses in a developmental toxicity study produced overt maternal toxicity). These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 12. Exposure route and method Were the route and method of exposure reported and suited to the test substance (e.g., was the test substance non-volatile in dietary studies)?		
High (score = 1)	The route and method of exposure were reported and were suited to the test substance. For inhalation studies, a dynamic chamber was used. While dynamic nose-only (or head-only) studies are generally preferred, dynamic whole-body chambers are acceptable for gases and for vapors that do not condense.	
Medium (score = 2)	There were minor limitations regarding the route and method of exposure, but the researchers took appropriate steps to mitigate the problem (e.g., mixed diet fresh each day for volatile compounds). These limitations are unlikely to have a substantial impact on results. For inhalation studies, a dynamic whole-body chamber was used for vapors that may condense or for aerosols.[28]	
Low (score = 3)	There were deficiencies regarding the route and method of exposure that are likely to have a substantial effect on results. Researchers may have attempted to correct the problem, but the success of the mitigating action was unclear. For inhalation studies, there are significant flaws in the design or operation of the inhalation chamber, such as uneven distribution of test substance in a whole-body chamber, having less than 15 air changes/hour in a whole-body chamber, or using a whole-body chamber that is too small for the number and volume of animals exposed.	
Unacceptable (score = 4)	The route or method of exposure was not reported **OR** an inappropriate route or method (e.g., administration of a volatile organic compound via the diet) was used for the test substance <u>without</u> taking steps to correct the problem (e.g., mixing fresh diet). These are serious flaws that makes the study unusable. For inhalation studies, either a static chamber was used, there is no description of the inhalation chamber, or an atypical exposure method was	

[28] This results in a medium score because in addition to inhalation exposure to the test substance, there may also be significant oral exposure due to rodents grooming test substance that adheres to their fur. The combined oral and inhalation exposure results in a lower POD, which makes a test substance appear more toxic than it really is by the inhalation route.

	used, such as allowing a container of test substance to evaporate in a room.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 4. Test Animals		
Metric 13. Test animal characteristics Were the test animal species, strain, sex, health status, age, and starting body weight reported? Was the test animal from a commercial source or in-house colony? Was the test species and strain an appropriate animal model for the evaluation of the specific outcome(s) of interest (e.g., routinely used for similar study types)?		
High (score = 1)	The test animal species, strain, sex, health status, age, and starting body weight were reported, and the test animal was obtained from a commercial source or laboratory-maintained colony. The test species and strain were an appropriate animal model for the evaluation of the specific outcome(s) of interest (e.g., routinely used for similar study types).	
Medium (score = 2)	Minor uncertainties in the reporting of test animal characteristics (e.g., health status, age, or starting body weight) are unlikely to have a substantial impact on results. The test animals were obtained from a commercial source or in-house colony, and the test species/strain/sex was an appropriate animal model for the evaluation of the specific outcome(s) of interest (e.g., routinely used for similar study types).	
Low (score = 3)	The source of the test animal was not reported **OR** the test animal strain or sex was not reported. These deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	The test animal species was not reported **OR** the test animal (species, strain, sex, life-stage, source) was not appropriate for the evaluation of the specific outcome(s) of interest (e.g., genetically modified animals, strain was uniquely susceptible or resistant to one or more outcome of interest). These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 14. Adequacy and consistency of animal husbandry conditions Were all husbandry conditions (e.g., housing, temperature) adequate and the same for control and exposed populations, such that the only difference was exposure to the test substance?		
High (score = 1)	All husbandry conditions were reported (e.g., temperature, humidity, light-dark cycle) and were adequate and the same for control and exposed populations, such that the only difference was exposure.	
Medium (score = 2)	Most husbandry conditions were reported and were adequate and similar for all groups. Some differences in conditions were identified among groups, but these differences were considered minor uncertainties or limitations that are unlikely to have a substantial impact on results.	
Low (score = 3)	Husbandry conditions were not sufficiently reported to evaluate if husbandry was adequate and if differences occurred between control and exposed populations. These deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	There were significant differences in husbandry conditions between control and exposed groups (e.g., temperature, humidity, light-dark cycle) **OR**	

	animal husbandry conditions deviated from customary practices in ways likely to impact study results (e.g., injuries and stress due to cage overcrowding). These are serious flaws that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 15. Number of animals per group Was the number of animals per study group appropriate for the study type and outcome analysis?		
High (score = 1)	The number of animals per study group was reported, appropriate for the study type and outcome analysis, and consistent with studies of the same or similar type (e.g., 50/sex/group for rodent cancer bioassay, 10/sex/group for rodent subchronic study, etc.).	
Medium (score = 2)	The reported number of animals per study group was lower than the typical number used in studies of the same or similar type (e.g., 30/sex/group for rodent cancer bioassay, 8/sex/group for rodent subchronic study, etc.), but sufficient for statistical analysis and this minor limitation is unlikely to have a substantial impact on results.	
Low (score = 3)	The reported number of animals per study group was not sufficient for statistical analysis (e.g., varying numbers per group with some groups consisting of only one animal) and this deficiency is likely to have a substantial impact on results.	
Unacceptable (score = 4)	The number of animals per study group was not reported **OR** the number of animals per study group was insufficient to characterize toxicological effects (e.g., 1-2 animals in each group). These are serious flaws that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 5. Outcome Assessment		
Metric 16. Outcome assessment methodology Did the outcome assessment methodology address or report the intended outcome(s) of interest? Was the outcome assessment methodology (including endpoints and timing of assessment) sensitive for the outcome(s) of interest (e.g., measured endpoints that are able to detect a true health effect or hazard)? Note: Outcome, as addressed in this domain, refers to health effects measured in an animal study (e.g., organ-specific toxicity, reproductive and developmental toxicity).		
High (score = 1)	The outcome assessment methodology addressed or reported the intended outcome(s) of interest and was sensitive for the outcomes(s) of interest.	
Medium (score = 2)	The outcome assessment methodology partially addressed or reported the intended outcomes(s) of interest (e.g., serum chemistry and organ weight evaluated in the absence of histology), but minor uncertainties are unlikely to have a substantial impact on results.	
Low (score = 3)	Significant deficiencies in the reported outcome assessment methodology were identified **OR** due to incomplete reporting, it was unclear whether methods were sensitive for the outcome of interest. This is likely to have a substantial impact on results.	
Unacceptable (score = 4)	The outcome assessment methodology was not reported **OR** the reported outcome assessment methodology was not sensitive for the	

	outcome(s) of interest (e.g., evaluation of endpoints outside the critical window of development, a systemic toxicity study that evaluated only grossly observable endpoints, such as clinical signs and mortality, etc.). These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 17. Consistency of outcome assessment Was the outcome assessment carried out consistently (i.e., using the same protocol) across study groups (e.g., assessment at the same time after initial exposure in all study groups)?		
High (score = 1)	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups (e.g., at the same time after initial exposure) using the same protocol in all study groups.	
Medium (score = 2)	There were minor differences in the timing of outcome assessment across study groups, or incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have substantial impact on results.	
Low (score = 3)	Details regarding the execution of the study protocol for outcome assessment (e.g., timing of assessment across groups) were not reported, and these deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups **OR** outcome assessments were not adequately reported for meaningful interpretation of results. These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 18. Sampling adequacy Was sampling adequate for the outcome(s) of interest, including experimental unit (e.g., litter vs. individual animal weight), number of evaluations per dose group, and endpoint (e.g., number of slides evaluated per organ)?		
High (score = 1)	Details regarding sampling for the outcome(s) of interest were reported and the study used adequate sampling for the outcome(s) of interest (e.g., litter data provided for developmental studies; endpoints were evaluated in an adequate number of animals in each group).	
Medium (score = 2)	Details regarding sampling for the outcome(s) of interest were reported, but minor limitations were identified in the sampling of the outcome(s) of interest (e.g., histopathology was performed for high-dose group and controls only, and treatment-related changes were observed at the high dose) that are unlikely to have a substantial impact on results.	
Low (score = 3)	Details regarding sampling of outcomes were not reported and this deficiency is likely to have a substantial impact on results.	
Unacceptable (score = 4)	Sampling was not adequate for the outcome(s) of interest (e.g., histopathology was performed on exposed groups, but not controls). This is a serious flaw that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important*	

	elements such as relevance]	
Metric 19. Blinding of assessors Were investigators assessing subjective outcomes (i.e., those evaluated using human judgment, including functional observational battery, qualitative neurobehavioral endpoints, histopathological re-evaluations) blinded to treatment group? If blinding was not applied, were quality control/quality assurance procedures for endpoint evaluation cited? Note that blinding is not required for initial histopathology review in accordance with Best Practices recommended by the Society of Toxicologic Pathology. This should be considered when rating this metric.[a] This metric is not rated/applicable for initial histopathology review or if no subjective outcomes were assessed (i.e., only automated measurements were included and/or human judgment was not applied).		
High (score = 1)	The study explicitly reported that investigators assessing subjective outcomes (i.e., those evaluated using human judgment, including functional observational battery, qualitative neurobehavioral endpoints, histopathological re-evaluations) were blinded to treatment group or that quality control/quality assurance methods were followed in the absence of blinding.	
Medium (score = 2)	The study reported that blinding was not possible, but steps were taken to minimize bias (e.g., knowledge of study group was restricted to personnel not assessing subjective outcome) and this minor uncertainty is unlikely to have a substantial impact on results. Alternately, blinding was not reported; however, lack of blinding is not expected to have a substantial impact on results.	
Low (score = 3)	The study did not report whether assessors were blinded to treatment group for subjective outcomes, and this deficiency is likely to have a substantial impact on results.	
Unacceptable (score = 4)	Information in the study report did not report whether assessors were blinded to treatment group for subjective outcomes or suggested that the assessment of subjective outcomes (e.g., functional observational battery, qualitative neurobehavioral endpoints, histopathological re-evaluations) was performed in a biased fashion (e.g., assessors of subjective outcomes were aware of study groups). This is a serious flaw that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 20. Negative control response Were the biological responses (e.g., histopathology, litter size, pup viability, etc.) of the negative control group(s) adequate?		
High (score = 1)	The biological responses of the negative control group(s) were adequate (e.g., no/low incidence of histopathological lesions).	
Medium (score = 2)	There were minor uncertainties or limitations regarding the biological responses of the negative control group(s) (e.g., differences in outcome between untreated and solvent controls) that are unlikely to have a substantial impact on results.	
Low (score = 3)	The biological responses of the negative control group(s) were reported, but there were deficiencies regarding the control responses that are likely to have a substantial impact on results (e.g., elevated incidence of histopathological lesions).	
Unacceptable (score = 4)	The biological responses of the negative control groups were not reported **OR** there was unacceptable variation in biological responses between control replicates. These are serious flaws that make the study unusable.	

Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 6. Confounding/Variable Control		
Metric 21 Confounding variables in test design and procedures Were there confounding differences among the study groups in initial body weight or test substance palatability that could influence the outcome assessment (e.g., did palatability issues lead to dehydration and/or malnourishment)? Did reflex bradypnea (i.e., reduced respiration and reduced test substance exposure) induced by respiratory irritants influence outcome assessment? Were normal signs of reflex bradypnea misinterpreted as neurologic, behavioral, or developmental effects (e.g. hypothermia, lethargy, unconsciousness, poor performance in behavioral studies, delayed pup development)?		
High (score = 1)	There were no reported differences among the study groups in initial body weight, food or water intake, or respiratory rate that could influence the outcome assessment.	
Medium (score = 2)	The study reported minor differences among the study groups (<20% difference from control) with respect to initial body weight, drinking water and/or food consumption due to palatability issues, or respiratory rate due to reflex bradypnea. These minor uncertainties are unlikely to have a substantial impact on results. Alternately, the lack of reporting of initial body weights, food/water intake, and/or respiratory rate is not likely to have a significant impact on results.	
Low (score = 3)	Initial body weight, food/water intake, and respiratory rate were not reported. These deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	The study reported significant differences among the study groups with respect to initial body weight, decreased drinking water/food intake due to palatability issues (≥20% difference from control) that could lead to dehydration and/or malnourishment, or reflex bradypnea that could lead to decreased oxygenation of the blood. These are serious flaws that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 22. Health outcomes unrelated to exposure Were there differences among the study groups in animal attrition or health outcomes unrelated to exposure (e.g., infection) that could influence the outcome assessment? Professional judgement should be used to determine whether or not signs of infection would invalidate the study. Criteria for High, Medium and Low are used when the study is still usable.		
High (score = 1)	Details regarding animal attrition and health outcomes unrelated to exposure (e.g., infection) were reported for each study group and there were no differences among groups that could influence the outcome	

	assessment.	
Medium (score = 2)	Authors reported that one or more study groups experienced disproportionate animal attrition or health outcomes unrelated to exposure (e.g., infection), but data from the remaining exposure groups were valid and the low incidence of attrition is unlikely to have a substantial impact on results **OR** data on attrition and/or health outcomes unrelated to exposure for each study group were not reported because only substantial differences among groups were noted (as indicated by study authors).	
Low (score = 3)	Data on attrition and/or health outcomes unrelated to exposure were not reported for each study group and this deficiency is likely to have a substantial impact on results. **OR** data on attrition and/or health outcomes are reported and could have substantial impact on results.	
Unacceptable (score = 4)	One or more study groups experienced serious animal attrition or health outcomes unrelated to exposure (e.g., infection). This is a serious flaw that makes the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 7. Data Presentation and Analysis		
Metric 23. Statistical methods Were statistical methods clearly described and appropriate for dataset(s) (e.g., parametric test for normally distributed data)?		
High (score = 1)	Statistical methods were clearly described and appropriate for dataset(s) (e.g., parametric test for normally distributed data). **OR** no statistical analyses, calculation methods, and/or data manipulation were conducted but sufficient data were provided to conduct an independent statistical analysis.	
Medium (score = 2)	Statistical analysis was described with some omissions that would unlikely have a substantial impact on results.	
Low (score = 3)	Statistical analysis was not described clearly, and this deficiency is likely to have a substantial impact on results.	
Unacceptable (score = 4)	Statistical methods were not appropriate (e.g., parametric test for non-normally distributed data) **OR** statistical analysis was not conducted **AND** data were not provided preventing an independent statistical analysis. These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 24. Reporting of data Were the data for all outcomes presented? Were data reported by exposure group and sex (if applicable), with numbers of animals affected and numbers of animals evaluated (for quantal data) or group means and variance (for continuous data)? If severity scores were used, was the scoring system clearly articulated?		
High (score = 1)	Data for exposure-related findings were presented for all outcomes by exposure group and sex (if applicable) with quantal and/or continuous presentation and description of severity scores if applicable. Negative	

	findings were reported qualitatively or quantitatively.	
Medium (score = 2)	Data for exposure-related findings were reported for most, but not all, outcomes by exposure group and sex (if applicable) with quantal and/or continuous presentation and description of severity scores if applicable. The minor uncertainties in outcome reporting are unlikely to have substantial impact on results.	
Low (score = 3)	Data for exposure-related findings were not shown for each study group, but results were described in the text and/or data were only reported for some outcomes. These deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	Data presentation was inadequate (e.g., the report does not differentiate among findings in multiple exposure groups) **OR** major inconsistencies were present in reporting of results. These are serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 8. Other (Apply as Needed)		
Metric:		
High (score = 1)		
Medium (score = 2)		
Low (score = 3)		
Unacceptable (score = 4)		
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

[a] Crissman et al. (2004)

G.5.2 *In Vitro* Toxicity Studies

Table G-15. Serious Flaws that Would Make *In Vitro* Toxicity Studies Unacceptable

Optimization of the list of serious flaws may occur after pilot calibration exercises.

Domain	Metric	Description of Serious Flaw(s) in Data Source[a]
Test Substance	Test Substance Identity	The test substance identity and form (if applicable) could not be determined from the information provided (e.g., nomenclature was unclear and CASRN or structure were not reported) **OR** the components and ratios of mixtures were not characterized.
	Test Substance Source	The test substance was not obtained from a manufacturer **OR** if synthesized or extracted, analytical verification of the test substance was not conducted.
	Test Substance Purity	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities.
Test Design	Negative Controls	A concurrent negative control group was not included or reported **OR** the reported negative control group was not appropriate (e.g., different cell lines used for controls and test substance exposure).
	Positive Controls	A concurrent positive control or proficiency group was not used (when applicable).
	Assay Procedures	Assay methods and procedures were not reported **OR** assay methods and procedures were not appropriate for the study type (e.g., *in vitro* skin corrosion protocol used for *in vitro* skin irritation assay).
	Standards for Testing	QC criteria were not reported and/or inadequate data were provided to demonstrate validity, acceptability, and reliability of the test when compared with current standards and guidelines.
Exposure Characterization	Preparation and Storage of Test Substance	Information on preparation and storage was not reported **OR** serious flaws reported with test substance preparation and/or storage conditions will have critical impacts on dose/concentration estimates and make the study unusable (e.g., instability of test substance in exposure media, test substance volatilized rapidly from the open containers that were used as test vessels).
	Consistency of Administration	Critical exposure details (e.g., amount of test substance used) were not reported **OR** exposures were not administered consistently across and/or within study groups (e.g., 75 mg/cm^2 and 87 mg/cm^2 administered to reconstructed corneas replicate 1 and replicate 2, respectively, in *in vitro* eye irritation test) resulting in serious flaws that make the study unusable.
	Reporting of Concentrations	The exposure doses/concentrations or amounts of test substance were not reported resulting in serious flaws.
	Exposure Duration	No information on exposure duration(s) was reported

		OR the exposure duration was not appropriate for the study type and/or outcome of interest (e.g., 5 hours for reconstructed epidermis in skin irritation test, 24 hours exposure for bacterial reverse mutation test).
	Number of Exposure Groups and Concentrations Spacing	The number of exposure groups and dose/concentration spacing were not reported **OR** the number of exposure groups and dose/concentration spacing were not relevant for the assessment (e.g., all concentrations used in an *in vitro* mammalian cell micronucleus test were cytotoxic).
	Metabolic Activation	No information on the characterization and use of a metabolic activation system was reported.
Test Model	Test Model	The test model and descriptive information were not reported **OR** the test model was not appropriate for evaluation of the specific outcome of interest (e.g., bacterial reverse mutation assay to evaluate chromosome aberrations).
	Number per Group	The number of organisms or tissues per study group and/or replicates per study group were not reported **OR** the number of organisms or tissues per study group and/or replicates per study group were insufficient to characterize toxicological effects (e.g., one tissue/test concentration/one exposure time for *in vitro* skin corrosion test, one replicate/strain of bacteria exposed in bacterial reverse mutation assay).
Outcome Assessment	Outcome Assessment Methodology	The outcome assessment methodology was not reported **OR** the assessment methodology was not appropriate for the outcome(s) of interest (e.g., cells were evaluated for chromosomal aberrations immediately after exposure to the test substance instead of after post-exposure incubation period, cytotoxicity not determined prior to CD86/CD expression measurement assay, and labeling antibodies were not tested on proficiency substances in an *in vitro* skin sensitization test in h-CLAT cells).
	Consistency of Outcome Assessment	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups **OR** outcome assessments were not adequately reported for meaningful interpretation of results.
	Sampling Adequacy	Reported sampling was not adequate for the outcome(s) of interest and/or serious uncertainties or limitations were identified in how the study carried out the sampling of the outcome(s) of interest (e.g., replicates from control and test concentrations were evaluated at different times).
	Blinding of Assessors	Information in the study report suggested that the assessment of subjective outcomes was performed in a biased fashion (e.g., assessors of subjective outcomes were aware of study groups).
Confounding/ Variable Control	Confounding Variables in Test Design and Procedures	There were significant differences among the study groups with respect to the strain/batch/lot number of organisms or models used per group or size and/or quality of tissues exposed (e.g., initial number of viable bacterial cells were different for each replicate [10^5 cells in replicate 1, 10^8 cell in replicate 2, and 10^3 cells in

		replicate 3], tissues from two different lots were used for *in vitro* skin corrosion test, but the control batch quality for one lot was outside of the acceptability range).
	Confounding Variables in Outcomes Unrelated to Exposure	One or more replicates or groups (i.e., negative and positive controls experienced disproportionate growth or reduction in growth unrelated to exposure (e.g., contamination) such that no outcomes could be assessed.
Data Presentation and Analysis	Data Analysis	Statistical methods, calculation methods, or data manipulation were not appropriate (e.g., Student's t-test used to compare 2 groups in a multi-group study, parametric test for non-normally distributed data) **OR** statistical analysis was not conducted **AND** data enabling an independent statistical analysis were not provided.
	Data Interpretation	The reported scoring and/or evaluation criteria were inconsistent with established practices resulting in the interpretation of data results that are seriously flawed.
	Cytotoxicity Data	Cytotoxicity endpoints were not defined, methods were not described, and it could not be determined that cytotoxicity was accounted for in the interpretation of study results.
	Reporting of Data	Data presentation was inadequate (e.g., the report did not differentiate among findings in multiple exposure groups, no scores or frequencies were reported), or major inconsistencies were present in reporting of results.

Note:
[a] If the metric does not apply to the study type, the flaw will not be applied to determine unacceptability.

Table G-16. Data Quality Criteria for *In Vitro* Toxicity Studies

Confidence Level (Score)	Description	Selected Score
Domain 1. Test Substance		
Metric 1. Test substance identity Was the test substance identified definitively (i.e., established nomenclature, CASRN, physical nature, physiochemical properties, and/or structure reported, including information on the specific form tested [e.g., salt or base, valence state, isomer, if applicable] for materials that may vary in form)? If test substance was a mixture, were mixture components and ratios characterized?		
High (score = 1)	The test substance was identified definitively (i.e., established nomenclature, CASRN, physical nature, physiochemical properties, and/or structure reported, including information on the specific form tested (e.g., salt or base, valence state, isomer, [if applicable]) for materials that may vary in form. For mixtures, the components and ratios were characterized.	
Medium (score = 2)	The test substance and form (if applicable) were identified, and components and ratios of mixtures were characterized, but there were minor uncertainties (e.g., minor characterization details were omitted) that are unlikely to have a substantial impact on results.	
Low (score = 3)	The test substance and form (if applicable) were identified, and components and ratios of mixtures were characterized, but there were uncertainties regarding test substance identification or characterization that are likely to have a substantial impact on the results.	
Unacceptable (score = 4)	The test substance identity and form (if applicable) could not be determined from the information provided (e.g., nomenclature was unclear and CASRN or structure were not reported) **OR** the components and ratios of mixtures were not characterized.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 2. Test substance source Was the source of the test substance reported, including manufacturer and batch/lot number for materials that may vary in composition? If synthesized or extracted, was test substance identity verified by analytical methods?		
High (score = 1)	The source of the test substance was reported, including manufacturer and batch/lot number for materials that may vary in composition, and its identity was certified by manufacturer and/or verified by analytical methods (melting point, chemical analysis, etc.).	
Medium (score = 2)	The source of the test substance and/or the analytical verification of a synthesized test substance was reported incompletely, but the omitted details are unlikely to have a substantial impact on the results.	
Low (score = 3)	Omitted details on the source of the test substance and/or analytical verification of a synthesized test substance are likely to have a substantial impact on the results.	
Unacceptable (score = 4)	The test substance was not obtained from a manufacturer **OR** if synthesized or extracted, analytical verification of the test substance was not conducted.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important*	

	elements such as relevance]	
Metric 3. Test substance purity Was the purity or grade (i.e., analytical, technical) of the test substance reported and adequate to identify its toxicological effects? Were impurities identified? Were impurities present in quantities that could influence the results?		
High (score = 1)	The test substance purity and composition were such that any observed effects were highly likely to be due to the nominal test substance itself (e.g., ACS grade, analytical grade, reagent grade test substance or a formulation comprising primarily inert ingredients with small amount of active ingredient). Impurities, if identified, were not present in quantities that could influence the results.	
Medium (score = 2)	Minor uncertainties or limitations were identified regarding the test substance purity and composition; however, the purity and composition were such that observed effects were more likely than not to be due to the nominal test substance and impurities, if identified, were unlikely to have a substantial impact on the results.	
Low (score = 3)	Purity and/or grade of test substance were not reported **OR** the percentage of the reported purity was such that the observed effects may not have been due to the nominal test substance.	
Unacceptable (score = 4)	The nature and quantity of reported impurities were such that study results were likely to be due to one or more of the impurities.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 2. Test Design		
Metric 4. Negative controls Was a concurrent negative (untreated, sham-treated, and/or vehicle, as necessary) control group included?		
High (score = 1)	Study authors reported using a concurrent negative control group (untreated, sham-treated, and/or vehicle, as applicable) in which all conditions equal except exposure to test substance.	
Medium (score = 2)	Study authors reported using a concurrent negative control group, but all conditions were not equal to those of treated groups; however, the identified differences are considered to be minor limitations that are unlikely to have substantial impact on results.	
Low (score = 3)	Study authors acknowledged using a concurrent negative control group, but details regarding the negative control group were not reported, and the lack of details is likely to have a substantial impact on the results.	
Unacceptable (score = 4)	A concurrent negative control group was not included or reported **OR** the reported negative control group was not appropriate (e.g., different cell lines used for controls and test substance exposure).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Metric 5. Positive controls Was a concurrent positive or proficiency control group included, *if applicable*, based on study type, and was the response appropriate in this group (e.g., induction of positive effect)? *This metric is applicable studies that require a concurrent positive control.		
High (score = 1)	A concurrent positive control or proficiency control group, if applicable, was used and the intended positive response was induced.	
Medium (score = 2)	A concurrent positive control or proficiency control was used, but there were minor uncertainties (e.g., minor details regarding control exposure or response were omitted) that are unlikely to have a substantial impact on results.	
Low (score = 3)	A concurrent positive control or proficiency control was used, but there were uncertainties regarding the control exposure or response that are likely to have a substantial impact on results (e.g., the control response was not described).	
Unacceptable (score = 4)	A concurrent positive control or proficiency group was not used.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 6. Assay procedures Were assay methods and procedures (e.g., test conditions, cell density culture media and volumes, pre- and post-incubation temperatures, humidity, reaction mix, washing/rinsing methods, incubation with amino acids, slide preparation, instrument used and calibration, wavelengths measured) described in detail and applicable to the study type?		
High (score = 1)	Study authors described the methods and procedures (e.g., test conditions, cell density culture media and volumes, pre- and post-incubation temperatures, humidity, reaction mix, washing/rinsing methods, incubation with amino acids, slide preparation, instrument used and calibration, wavelengths measured) used for the test in detail and they were applicable for the study type (e.g., protocol for *in vitro* skin irritation test was reported).	
Medium (score = 2)	Methods and procedures were partially described and/or cited in another publication(s), but appeared to be appropriate (e.g., reporting that "calculations were used for enumerating viable and mutant cells" in a mammalian cell gene mutation test using *Hprt* and *xprt* genes instead of inclusion of the equations) to the study type, so the omission is unlikely to have a substantial impact on results.	
Low (score = 3)	The methods and procedures were not well described or deviated from customary practices (e.g., post-incubation time was not stated in a mammalian cell gene mutation test using *Hprt* and *xprt* genes) and this is likely to have a substantial impact on results.	
Unacceptable (score = 4)	Assay methods and procedures were not reported **OR** assay methods and procedures were not appropriate for the study type (e.g., *in vitro* skin corrosion protocol used for *in vitro* skin irritation assay).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 7. Standards for tests		

For assays with established criteria, were the test validity, acceptability, reliability, and/or QC criteria reported and consistent with current standards and guidelines? Example acceptability and QC criteria for an *in vitro* skin corrosion test using the EpiSkin™ (SM) model: Acceptability criteria: negative control OD values between ≥0.6 and ≤1.5, variability of the positive control replicates should be ≤20% of negative control, difference of viability between 2 tissue replicates should not exceed 30% in the range of 20-100% viability and for EDs≥0.3; QC criteria: Only QC-accepted tissue batches having an IC_{50} range of 1.0-3.0 mg/mL were used.) * This metric is generally applicable to studies using reconstructed human cells and may not be applicable to other studies.		
High (score = 1)	The test validity, acceptability, reliability, and/or QC criteria were reported and consistent with current standards and guidelines,[a] if applicable.	
Medium (score = 2)	Not applicable for this metric.	
Low (score = 3)	Not applicable for this metric.	
Unacceptable (score = 4)	QC criteria were not reported and/or inadequate data were provided to demonstrate validity, acceptability, and reliability of the test when compared with current standards and guidelines.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Exposure Characterization		
Metric 8. Preparation and storage of test substance Did the study characterize preparation of the test substance and storage conditions? Were the frequency of preparation and/or storage conditions appropriate to the test substance stability and solubility (if applicable)?		
High (score = 1)	The test substance preparation and/or storage conditions (e.g., test substance stability, homogeneity, mixing temperature, stock concentration, stirring methods, centrifugation/filtration, aerosol/vapor generation method, storage conditions) were reported and appropriate (e.g., stability in exposure media confirmed, volatile test substances prepared and stored in sealed containers) for the test substance.	
Medium (score = 2)	The test substance preparation and storage conditions were reported, but minor limitations in the test substance preparation and/or storage conditions were identified (e.g., test substance formulations were stirred instead of centrifuged for a specific number of rotations per minute) that are unlikely to have a substantial impact on results.	
Low (score = 3)	Deficiencies in reporting of test substance preparation, and/or storage conditions are likely to have a substantial impact on results (e.g., available information on physical-chemical properties suggests that stability and/or solubility of test substance in vehicle or culture media may be poor).	
Unacceptable (score = 4)	Information on preparation and storage was not reported **OR** serious flaws reported with test substance preparation and/or storage conditions will have critical impacts on dose/concentration estimates and make the study unusable (e.g., instability of test substance in exposure media, test substance volatilized rapidly from the open containers that were used as test vessels).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Metric 9. Consistency of administration Were exposures administered consistently across study groups (e.g., consistent application methods and volumes, control for evaporation)?		
High (score = 1)	Details of exposure administration were reported and exposures were administered consistently across study groups in a scientifically sound manner (e.g., consistent application methods and volumes, control for evaporation).	
Medium (score = 2)	Details of exposure administration were reported or inferred from the text, but the minor limitations in administration of exposures (e.g., accidental mistakes in dosing) that were identified are unlikely to have a substantial impact on results.	
Low (score = 3)	Details of exposure administration were reported, but deficiencies in administration of exposures (e.g., non-calibrated instrument used to administer test substance) that were reported or inferred from the text are likely to have a substantial impact on results.	
Unacceptable (score = 4)	Critical exposure details (e.g., amount of test substance used) were not reported **OR** exposures were not administered consistently across and/or within study groups (e.g., 75 mg/cm^2 and 87 mg/cm^2 administered to reconstructed corneas replicate 1 and replicate 2, respectively, in *in vitro* eye irritation test) resulting in serious flaws that make the study unusable.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 10. Reporting of concentrations Were exposure doses/concentrations or amounts of test substance reported without ambiguity (e.g., point estimate instead of range, analytical instead of nominal)?		
High (score = 1)	The exposure doses/concentrations or amounts of test substance were reported without ambiguity (e.g., point estimate instead of range, analytical instead of nominal).	
Medium (score = 2)	Not applicable for this metric.	
Low (score = 3)	Not applicable for this metric.	
Unacceptable (score = 4)	The exposure doses/concentrations or amounts of test substance were not reported resulting in serious flaws.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 11. Exposure duration Was the exposure duration (e.g., minutes, hours, days) reported and appropriate for this study type and/or outcome(s) of interest?		
High (score = 1)	The exposure duration (e.g., min, hours, days) was reported and appropriate for the study type and/or outcome(s) of interest (e.g., 60-minute exposure for reconstructed epidermis in skin irritation test, 48-72-hour exposure for bacterial reverse mutation assay).	
Medium (score = 2)	Duration(s) of exposure differed slightly from current standards and guidelines[a] for studies of this type (e.g., 65 minutes for reconstructed epidermis in skin irritation test), but the differences are unlikely to have a	

	substantial impact on results.	
Low (score = 3)	Duration(s) of exposure were not clearly stated (e.g., exposure duration was described only in qualitative terms) or duration(s) differed significantly from studies of the same or similar types. These deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	No information on exposure duration(s) was reported **OR** the exposure duration was not appropriate for the study type and/or outcome of interest (e.g., 5 hours for reconstructed epidermis in skin irritation test, 24 hours exposure for bacterial reverse mutation test).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 12. Number of exposure groups and concentrations spacing Were the number of exposure groups and dose/concentration spacing justified by study authors (e.g., based on study type, range-finding study, and/or cytotoxicity studies) and adequate to address the purpose of the study (e.g., to evaluate dose-response relationships, inform MOA/AOP)?		
High (score = 1)	The number of exposure groups and dose/concentration spacing were justified by study authors (e.g., based on study type, range-finding study, and/or cytotoxicity studies) and considered adequate to address the purpose of the study (e.g., to evaluate dose-response relationships, inform MOA/AOP).	
Medium (score = 2)	There were minor limitations regarding the number of exposure groups and/or dose/concentration spacing, but the number of exposure groups and spacing of exposure levels were adequate to show results relevant to the outcome of interest (e.g., observation of a dose-response relationship) and the concerns are unlikely to have a substantial impact on results.	
Low (score = 3)	There were deficiencies regarding the number of exposure groups and/or dose/concentration spacing (e.g., one bacterial strain exposed to 2 concentrations of the test substance in bacterial reverse mutation assay) and these concerns were likely had a substantial impact on interpretation of the results.	
Unacceptable (score = 4)	The number of exposure groups and dose/concentration spacing were not reported **OR** the number of exposure groups and dose/concentration spacing were not relevant for the assessment (e.g., all concentrations used in an *in vitro* mammalian cell micronucleus test were cytotoxic).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 13. Metabolic activation (if applicable) Were exposures conducted in the presence and absence of a metabolic activation system, if applicable, for the study type? Were the source, method of preparation, concentration or volume in final culture, and quality control information on the metabolic activation system reported?		
High (score = 1)	Study authors reported exposures were conducted in the presence of metabolic activation and the type and source, method of preparation, concentration or volume in final culture, and quality control information of the metabolic activation system were described.	
Medium	The presence of a commonly used metabolic activation system (e.g., aroclor-	

(score = 2)	, ethanol-, or phenobarbitial/β-naphthoflavone-induced rat, hamster, or mice liver cells) was reported in the study; however, some details regarding type, composition mix, concentration, or quality control information were not described. These omissions are unlikely to have a substantial impact on the results.	
Low (score = 3)	The presence of a metabolic activation system was reported in the study, but the system described was not validated (e.g., rigorous testing to ensure that it suitable for the purpose for which it is used) or comparable to commonly used systems (e.g., aroclor-, ethanol-, or phenobarbitial/β-naphthoflavone-induced rat, hamster, or mice liver cells).	
Unacceptable (score = 4)	No information on the characterization and use of a metabolic activation system was reported.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 4. Test Model		
Metric 14. Test model Were the test models (e.g., cell types or lines, tissue models) and descriptive information (e.g., tissue origin, number of passages, karyotype features, doubling times, donor information, biomarkers) reported? Was the test model from a commercial source or an in-house culture? Was the model routinely used for the outcome of interest (e.g., Chinese hamster ovary cells for micronucleus formation)?		
High (score = 1)	The test model (e.g., cell types or lines, tissue models) and descriptive information (e.g., tissue origin, number of passages, karyotype features, doubling times, donor information, biomarkers) were reported, the test model was obtained from a commercial source or laboratory-maintained culture, and the test model was routinely used for the outcome of interest (e.g., Chinese hamster ovary cells for micronucleus formation).	
Medium (score = 2)	The test model was reported along with limited descriptive information. The test model was routinely used for the outcome of interest. Reporting limitations are unlikely to have a substantial impact on results.	
Low (score = 3)	The test model was reported but no additional details were reported **AND/OR** the test model was not routinely used for the outcome of interest (e.g., feline cell line for micronucleus formation). This is likely to have a substantial impact on results.	
Unacceptable (score = 4)	The test model and descriptive information were not reported **OR** the test model was not appropriate for evaluation of the specific outcome of interest (e.g., bacterial reverse mutation assay to evaluate chromosome aberrations).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 15. Number per group Was the number of organisms or tissues per study group and/or replicates per study group reported and appropriate for the study type and outcome analysis?		
High (score = 1)	The number of organisms or tissues per study group and/or number of replicates per study group were reported and were appropriate[a] for the study type and outcome analysis, and consistent with studies of the same or similar type (e.g., at least two replicates/test substance/3 different	

	exposure times for *in vitro* skin corrosion test, 3 replicates/strain of bacteria in bacterial reverse mutation assay).	
Medium (score = 2)	The number of organisms or tissues per study group and/or replicates per study group were reported but were lower than the typical number used in studies of the same or similar type (e.g., 3 replicates/strain of bacteria in bacterial reverse mutation assay), but were sufficient for analysis and unlikely to have a substantial impact on results.	
Low (score = 3)	The number of organisms or tissues per study group and/or replicates per study group were reported but were less than recommended by current standards and guidelines[a] (e.g., one tissue/test concentration/exposure time for *in vitro* skin corrosion test). This is likely to have a substantial impact on results.	
Unacceptable (score = 4)	The number of organisms or tissues per study group and/or replicates per study group were not reported **OR** the number of organisms or tissues per study group and/or replicates per study group were insufficient to characterize toxicological effects (e.g., one tissue/test concentration/one exposure time for *in vitro* skin corrosion test, one replicate/strain of bacteria exposed in bacterial reverse mutation assay).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 5. Outcome Assessment		
Metric 16. Outcome assessment methodology Did the outcome assessment methodology address or report the intended outcome(s) of interest? Was the outcome assessment methodology (including endpoints and timing of assessment) sensitive for the outcome(s) of interest (e.g., measured endpoints that are able to detect a true effect)?		
High (score = 1)	The outcome assessment methodology addressed or reported the intended outcome(s) of interest and was sensitive for the outcome(s) of interest.	
Medium (score = 2)	The outcome assessment methodology used only partially addressed or reported the intended outcomes(s) of interest (e.g., mutation frequency evaluated in the absence of cytotoxicity in a gene mutation test), but minor uncertainties are unlikely to have a substantial impact on results.	
Low (score = 3)	Significant deficiencies in the reported outcome assessment methodology were identified (e.g., optimum time for expression of chromosomal aberrations after exposure to test compound was not determined) **OR** due to incomplete reporting, it was unclear whether methods were sensitive for the outcome of interest. This is likely to have a substantial impact on results.	
Unacceptable (score = 4)	The outcome assessment methodology was not reported **OR** the assessment methodology was not appropriate for the outcome(s) of interest (e.g., cells were evaluated for chromosomal aberrations immediately after exposure to the test substance instead of after post-exposure incubation period).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Metric 17. Consistency of outcome assessment Was the outcome assessment carried out consistently (i.e., using the same protocol) across study groups (e.g., assessment at the same time after initial exposure in all study groups)?		
High (score = 1)	Details of the outcome assessment protocol were reported and outcomes were assessed consistently across study groups (e.g., at the same time after initial exposure) using the same protocol in all study groups.	
Medium (score = 2)	There were minor differences in the timing of outcome assessment across study groups, or incomplete reporting of minor details of outcome assessment protocol execution, but these uncertainties or limitations are unlikely to have substantial impact on results.	
Low (score = 3)	Details regarding the execution of the study protocol for outcome assessment (e.g., timing of assessment across groups) were not reported, and these deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	There were large inconsistencies in the execution of study protocols for outcome assessment across study groups **OR** outcome assessments were not adequately reported for meaningful interpretation of results.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 18. Sampling adequacy Was the reported sampling adequate for the outcome(s) of interest, including number of evaluations per exposure group, and endpoint (e.g., number of replicates/slides/cells/metaphases evaluated per test concentration)?		
High (score = 1)	The study reported adequate sampling for the outcome(s) of interest including number of evaluations per exposure group, and endpoint (e.g., number of replicates/slides/cells/metaphases [at least 300 well-spread metaphases scored/concentration in a chromosome aberration test]).	
Medium (score = 2)	Details regarding sampling for the outcome(s) of interest were reported, but minor limitations were identified in the reported sampling of the outcome(s) of interest, but those are unlikely to have a substantial impact on results.	
Low (score = 3)	Details regarding sampling of outcomes were not fully reported and the omissions are likely to have a substantial impact on results.	
Unacceptable (score = 4)	Reported sampling was not adequate for the outcome(s) of interest and/or serious uncertainties or limitations were identified in how the study carried out the sampling of the outcome(s) of interest (e.g., replicates from control and test concentrations were evaluated at different times).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 19. Blinding of assessors Were investigators assessing subjective outcomes (i.e., those evaluated using human judgment) blinded to treatment group? This metric is not rated/applicable if no subjective outcomes were assessed (i.e., only automated measurements were included and human judgment was not applied).		
High (score = 1)	The study explicitly reported that investigators assessing subjective outcomes (i.e., those evaluated using human judgment) were blinded to	

	treatment group or that quality control/quality assurance methods were followed in the absence of blinding.	
Medium (score = 2)	The study reported that blinding was not possible, but steps were taken to minimize bias (e.g., knowledge of study group was restricted to personnel not assessing subjective outcome) and this minor uncertainty is unlikely to have a substantial impact on results.	
Low (score = 3)	The study did not report whether assessors were blinded to treatment group for subjective outcomes, and this deficiency is likely to have a substantial impact on results.	
Unacceptable (score = 4)	Information in the study report suggested that the assessment of subjective outcomes was performed in a biased fashion (e.g., assessors of subjective outcomes were aware of study groups).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 6. Confounding/Variable Control		
Metric 20. Confounding variables in test design and procedures Were there confounding differences among the study groups in the strain/batch/lot number of organisms or models used per group, size, and/or quality of tissues exposed, or lot of test substance used that could influence the outcome assessment?		
High (score = 1)	There were no differences reported among study group parameters (e.g., test substance lot or batch, strain/batch/ lot number of organisms or models used per group or size, and/or quality of tissues exposed) that could influence the outcome assessment.	
Medium (score = 2)	Minor differences were reported in initial conditions that are unlikely to have a substantial impact on results (e.g., tissues from two different lots were used for *in vitro* skin corrosion test, and QC data were similar for both lots).	
Low (score = 3)	Initial strain/batch/lot number of organisms or models used per group, size, and/or quality of tissues exposed was not reported. These deficiencies are likely to have a substantial impact on results.	
Unacceptable (score = 4)	There were significant differences among the study groups with respect to the strain/batch/lot number of organisms or models used per group or size and/or quality of tissues exposed (e.g., initial number of viable bacterial cells were different for each replicate [10^5 cells in replicate 1, 10^8 cell in replicate 2, and 10^3 cells in replicate 3], tissues from two different lots were used for *in vitro* skin corrosion test, but the control batch quality for one lot was outside of the acceptability range).	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 21. Confounding variables in outcomes unrelated to exposure Were there differences among the study groups unrelated to exposure to test substance (e.g., contamination) that could influence the outcome assessment? Did the test material interfere in the assay (e.g., altering fluorescence or absorbance, signal quenching by heavy metals, altering pH, solubility or stability issues)?		
High (score = 1)	There were no reported differences among the study replicates or groups in test model unrelated to exposure (e.g., contamination) and the test substance did not interfere with the assay (e.g., signal quenching by heavy metals).	

Medium (score = 2)	Authors reported that one or more replicates or groups experienced disproportionate outcomes unrelated to exposure (e.g., contamination), but data from the remaining exposure replicates or groups were valid and is unlikely to have a substantial impact on results **OR** data on experienced disproportionate outcomes unrelated to exposure were not reported because only substantial differences among groups were noted (as indicated by study authors). **OR** the test material interfered in the assay, but the interference did not cause substantial differences among the groups..	
Low (score = 3)	Data on outcome differences unrelated to exposure were not reported for each study replicate or group. Assay interference was present or inferred resulting in large variabilities among the groups. The absence of this information is likely to have a substantial impact on results.	
Unacceptable (score = 4)	One or more replicates or groups (i.e., negative and positive controls experienced disproportionate growth or reduction in growth unrelated to exposure (e.g., contamination), or assay interference occurred such that no outcomes could be assessed.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 7. Data Presentation and Analysis		
Metric 22. Data analysis Were statistical methods, calculations methods, and/or data manipulation clearly described and appropriate for dataset(s)?		
High (score = 1)	Statistical methods, calculation methods, and/or data manipulation were clearly described and presented for dataset(s) (e.g., frequencies of chromosomal aberrations were statistically analyzed across groups, trend test used to determine dose relationships, or results compared to historical negative control data). **OR** no statistical analyses, calculation methods, and/or data manipulation were conducted but sufficient data were provided to conduct an independent statistical analysis.	
Medium (score = 2)	Statistical analysis was described with some omissions that would unlikely have a substantial impact on results.	
Low (score = 3)	Statistical analysis was not described clearly, and this deficiency is likely to have a substantial impact on results.	
Unacceptable (score = 4)	Statistical methods were not appropriate (e.g., Student's t-test used to compare 2 groups in a multi-group study, parametric test for non-normally distributed data) **OR** statistical analysis was not conducted **AND** data were not provided preventing an independent statistical analysis.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 23. Data interpretation Were the scoring and/or evaluation criteria reported and consistent with standards and guidelines?		

High (score = 1)	Study authors reported the scoring and/or evaluation criteria (e.g., for determining negative, positive, and equivocal outcomes) for the test and these were consistent with established practices.[a]	
Medium (score = 2)	Scoring and/or evaluation criteria were partially reported (e.g., evaluation criteria were reported following 3- and 60-minute exposures, but not for 240-minute exposure in *in vitro* skin corrosion test), but the omissions are unlikely to have a substantial impact on results.	
Low (score = 3)	Scoring and/or evaluation criteria were not reported and the omissions are likely to have a substantial impact on interpretation of the results.	
Unacceptable (score = 4)	The reported scoring and/or evaluation criteria were inconsistent with established practices. resulting in the interpretation of data results that are seriously flawed.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 24. Cytotoxicity data Were cytotoxicity endpoints defined, if necessitated by study type, and were methods for measuring cytotoxicity described and commonly used for assessment[a]?		
High (score = 1)	Study authors defined cytotoxicity endpoints (e.g., cell integrity, apoptosis, necrosis, color induction, cell viability, mitotic index) and the methods for measuring cytotoxicity were clearly described and commonly used for assessment.	
Medium (score = 2)	Cytotoxicity endpoints were defined and methods of measurement were partially reported, but the omissions are unlikely to have substantial impact on study results.	
Low (score = 3)	Cytotoxicity endpoints were defined, but the methods of measurements were not fully described or reported, and the omissions are likely to have a substantial impact on the study results.	
Unacceptable (score = 4)	Cytotoxicity endpoints were not defined, methods were not described, and it could not be determined that cytotoxicity was accounted for in the interpretation of study results.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 25. Reporting of data Were the data for all outcomes presented? Were data reported by exposure group?		
High (score = 1)	Data for exposure-related findings were presented for all outcomes by exposure group. Negative findings were reported qualitatively or quantitatively.	
Medium (score = 2)	Data for exposure-related findings were reported for most, but not all, outcomes by exposure group (e.g., sensitization percentages reported in the absence of incidence data). The minor uncertainties in outcome reporting are unlikely to have substantial impact on results.	
Low (score = 3)	Data for exposure-related findings were not shown for each study group, but results were described in the text and/or data were only reported for some outcomes. These deficiencies are likely to have a substantial impact on results.	

Unacceptable (score = 4)	Data presentation was inadequate (e.g., the report did not differentiate among findings in multiple exposure groups, no scores or frequencies were reported), or major inconsistencies were present in reporting of results.	
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 8. Other (Apply as Needed)		
Metric:		
High (score = 1)		
Medium (score = 2)		
Low (score = 3)		
Unacceptable (score = 4)		
Not rated/applicable		
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Note:

[a] For comparison purposes, current standards and guidelines may be reviewed at http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788; https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances; https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm#TOC.

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APPENDIX H: DATA QUALITY CRITERIA FOR EPIDEMIOLOGICAL STUDIES

H.1 Types of Data Sources

The data quality will be evaluated for the epidemiological studies listed in Table H-1.

Table H-1. Types of Epidemiological Studies

Data Category	Types of Data Sources
Epidemiological Studies	Controlled exposure, cohort, case-control, cross-sectional, case-crossover

H.2 Data Quality Evaluation Domains

The data sources will be evaluated against the following six data quality evaluation domains: study participation, exposure characterization, outcome assessment, potential confounding/variability control, analysis, and other. These domains, as defined in Table H-2, address elements of TSCA Science Standards 26(h)(1) through 26(h)(5).

Table H-2. Data Evaluation Domains and Definitions

Evaluation Domain	Definition
Study Participation	Study design elements characterizing the selection of participants in or out of the study (or analysis sample), which influence whether the exposure-outcome distribution among participants is representative of the exposure-outcome distribution in the overall population of eligible persons.
Exposure Characterization	Evaluation of exposure assessment methodology that includes consideration of methodological quality, sensitivity, and validation of the methods used, degree of variation in participants, and an established time order between exposure and outcome.
Outcome Assessment	Evaluation of outcome (effect) assessment methodology that includes consideration of diagnostic methods, training of interviewers, data sources including registries, blinding to exposure status or level, and reporting of all results.
Potential Confounding / Variability Control	Valid and reliable methods to reduce research-specific bias, including standardization, matching, adjustment in multivariate models, and stratification. This includes control of potential co-exposures when it is known that there is potential for co-exposure to occur and the co-exposure could influence the outcome of interest.
Analysis	Appropriate study design chosen for the research question with evaluation of statistical power, reproducibility, and statistical or modelling approaches.
Other / Consideration for Biomarker Selection and Measurement	Measures of biomarker (exposure and/or effect) data reliability. This includes but is not limited to evaluations of storage, stability and contamination of samples, validity and limits of detection of methods, method requirements, inclusion of matrix-specific considerations, and relationship of biomarker with external exposure, internal dose, or target dose.

H.3 Data Quality Evaluation Metrics

The data quality evaluation domains are evaluated by assessing two to seven unique metrics. Each metric is binned into a confidence level of *High*, *Medium*, *Low*, and/or Unacceptable. Each confidence level is assigned a numerical score (i.e., 1 through 4) that is used in the method of assessing the overall quality of the study.

A summary of the number of metrics and metric name for each data type is provided in Table H-3. Each domain has between 2 and 7 metrics. Metrics may be modified as EPA/OPPT acquires experience with the evaluation tool to support fit-for-purpose TSCA risk evaluations. Any modifications will be documented.

Detailed tables showing confidence level specifications of the metrics are provided in Tables H-6 through H-8 for each data type, including separate tables which summarize the serious flaws which would make the data source unacceptable for use in the hazard assessment.

Table H-3. Summary of Metrics for the Seven Data Types

Evaluation Domain	Number of Metrics Overall	Metrics (Metric Number and Description)
Study Participation	3	• Metric 1: Participant Selection • Metric 2: Attrition • Metric 3: Comparison Group
Exposure Characterization	3	• Metric 4: Measurement of Exposure • Metric 5: Exposure Levels • Metric 6: Temporality
Outcome Assessment	2	• Metric 7: Outcome Measurement or Characterization, • Metric 8: Reporting Bias
Potential Confounding / Variability Control	3	• Metric 9: Covariate Adjustment • Metric 10: Covariate Characterization • Metric 11: Co-exposure Counfounding/Moderation/Mediation
Analysis	4	• Metric 12: Study Design and Methods • Metric 13: Statistical Power • Metric 14: Reproducibility of Analyses • Metric 15: Statistical Models
Other / Consideration for Biomarker Selection and Measurement	7	• Metric 16: Use of Biomarker of Exposure • Metric 17: Effect Biomarker • Metric 18: Method Sensitivity • Metric 19: Biomarker Stability • Metric 20: Sample Contamination • Metric 21: Method Requirements • Metric 22: Matrix Adjustment

H.4 Scoring Method and Determination of Overall Data Quality Level

A scoring system is used to assign the overall quality of the data source, as discussed in Appendix A. Each data source is assigned an overall qualitative confidence level of *High*, *Medium*, *Low*, or *Unacceptable*. This section provides details about the scoring system that will be applied to epidemiologic studies, including the weighting factors assigned to each metric score of each domain.

H.4.1 Weighting Factors

The weighting method assumes that each domain carries an equal amount of weight of 1. However, some metrics within a given domain are given greater weights than others in the same domain, if they are regarded as key or critical metrics. Thus, EPA will use a weighting approach to reflect that some metrics are more important than others when assessing the overall quality of the epidemiologic data.

Each key or critical metric is assigned a higher weighting factor. The critical metrics are identified based on professional judgment in conjunction with consideration of the factors that are most frequently included in other study quality/risk of bias tools for epidemiologic literature. In developing metrics for each domain, several basic elements for epidemiologic studies were incorporated to form the structure of the 6 domains (Blumentthal et al. 2001), each of which are considered to be equally important aspects of an epidemiologic study.

The critical metrics within each domain are those that cover the most important aspects of the domain and are those that more directly evaluate the role of confounding and bias. After pilot testing the evaluation tool, EPA recognized that more attention (or weight) should be given to studies that measure exposure and disease accurately and allow for the consideration of potential confounding factors. Therefore, metrics deemed as critical metrics are those that identify the major biases associated with the domain, evaluate the measurement of exposure and disease, and/or address any potential confounding.

EPA/OPPT assigned a weighting factor that is twice the value of the other metrics within the same domain to each critical metric. Remaining metrics are assigned a weighting factor of 0.5 times the weighting factor assigned to the critical metric(s) in the domain. The sum of the weighting factors for each domain equals one. Tables H-4 identifies the critical metrics for epidemiologic studies, respectively, and provides a rationale for why the metrics are considered to be of greater importance than others within the domain. Table H-5 identifies the weighting factors assigned to each metric for epidemiologic studies, respectively.

Table H-4. Epidemiology Metrics with Greater Importance in the Evaluation and Rationale for Selection

Domain	Critical Metrics with Higher Weighting Factors (Metric Number) [a]	Rationale
Study Participation Study Participation	Participant Selection (Metric 1)	The participants selected for the study must be representative of the target population. Differences between participants and nonparticipants determines the amount of bias present, and differences should be well-described (Galea and Tracy 2007).
	Attrition (Metric 2)	Study attrition threatens the internal validity of studies, affects sample size, and compromises the precision of the measured associations (Kristman et al. 2004).
Exposure characterization	Measurement of Exposure (Metric 4)	The exposure of interest of should be well-defined and measured in a manner that is accurate, precise, and reliable to ensure the internal and external validity of the study findings (Blumenthal et al. 2001, Nieuwenhuijsen 2015).
	Temporality (Metric 6)	Temporality is essential to causal inference. Details must be provided to ensure the exposure sufficiently preceded the outcome and that enough time has passed since the exposure to observed said effect (Fedak et al. 2015).
Outcome assessment	Outcome Measurement or Characterization (Metric 7)	The methods used for outcome assessment must be fully described, valid, and sensitive to ensure that the observed effects are true, and to enable valid comparisons across studies (Blumenthal et al. 2001).
Potential Confounding/ variable control	Covariate Adjustment (Metric 9)	Control for confounding variables either through study design or analysis is considered important to ensure that any observed effects are attributable to the chemical exposure of interest and not to other factors (Blumenthal et al. 2001).
Analysis	Study Design and Methods (Metric 12)	The study design selected and applied analytical techniques for the collected data must be suitable to address the research question at hand (Checkoway et al. 2007).

[a]For the remaining metrics within the same domain, a weighting factor of 0.5*the key metric weighting factor is assigned

H.4.2 Calculation of Overall Study Score

A confidence level (1, 2, or 3 for High, Medium, or Low confidence, respectively) is assigned for each relevant metric within each domain. To determine the overall study score, the first step is to multiply the score for each metric (1, 2, or 3 for High, Medium, or Low confidence, respectively) by the appropriate weighting factor to obtain a weighted metric score. The weighted metric scores are then summed and divided by the sum of the weighting factors (for all metrics that are scored) to obtain an overall study score between 1 and 3. The equation for calculating the overall score is shown below:

$$\textit{Overall Score (range of 1 to 3)} = \sum (\textit{Metric Score} \times \textit{Weighting Factor}) / \sum (\textit{Weighting Factors})$$

Tables H-5 and H-6 present a summary of the domain, metrics and weighting approach for epidemiological studies with or without biomarkers, respectively. Table H-7 provides a scoring example for epidemiological studies where sample size is not applicable.

EPA/OPPT plans to use data with an overall quality level of *High, Medium*, or *Low* confidence to quantitatively or qualitatively support the risk evaluations, but does not plan to use data rated as *Unacceptable*. Studies with any single metric scored as 4 will be automatically assigned an overall quality score of *Unacceptable* and further evaluation of the remaining metrics is not necessary. An *Unacceptable* score means that serious flaws are noted in the domain metric that consequently make the data unusable (or invalid).

Any metrics that are *Not rated/not applicable* to the study under evaluation are not considered in the calculation of the study's overall quality score. These metrics are not included in the nominator or denominator of the *overall score* equation. The overall score is calculated using only those metrics that receive a numerical score. In addition, if a publication reports more than one study or endpoint, each study and, as needed, each endpoint will be evaluated separately.

Detailed tables showing quality criteria for the metrics are provided in Tables H-8 and H-9, including a table that summarizes the serious flaws that would make the data unacceptable for use in the human health hazard assessment.

Table H-5. Summary of Domain, Metrics, and Weighting Approach with Biomarkers

Domain	Metric	Range of Metric Scores	Metric weighting Factor	Domain Weight	Range of Weighted Metric Scores
Study Participation	Participant Selection	1 to 3	0.4	1	0.4 to 1.2
	Attrition	1 to 3	0.4		0.4 to 1.2
	Comparison Group	1 to 3	0.2		0.2 to 0.6
Exposure Characterization	Measurement of Exposure	1 to 3	0.4	1	0.4 to 1.2
	Exposure Levels	1 to 3	0.2		0.2 to 0.6
	Temporality	1 to 3	0.4		0.4 to 1.2
Outcome Assessment	Outcome measurement or characterization	1 to 3	0.67	1	0.67 to 2.01
	Reporting Bias	1 to 3	0.33		0.33 to 0.99
Potential Confounding/ Variable Control	Covariate Adjustment	1 to 3	0.5	1	0.5 to 1.5
	Covariate Characterization	1 to 3	0.25		0.25 to 0.75
	Co-exposure Confounding/Moderation/ Mediation	1 to 3	0.25		0.25 to 0.75
Analysis	Study Design and Methods	1 to 3	0.4	1	0.4 to 1.2
	Statistical Power	1 to 3	0.2		0.2 to 0.6
	Reproducibility of Analyses	1 to 3	0.2		0.2 to 0.6
	Statistical Models	1 to 3	0.2		0.2 to 0.6
Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al., 2014)	Use of Biomarker of Exposure	1 to 3	0.143	1	0.143 to 0.429
	Effect Biomarker	1 to 3	0.143		
	Method Sensitivity	1 to 3	0.143		
	Biomarker Stability	1 to 3	0.143		
	Sample Contamination	1 to 3	0.143		
	Method Requirements	1 to 3	0.143		
	Matrix Adjustment	1 to 3	0.143		
Equation: Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor				*Sum of Weighted Scores = 6 to 18* *Sum of Metric Weighting Factors= 6* 6/6=1; 18/6=3 Range of overall	

Table H-6. Summary of Domain, Metrics, and Weighting Approach for Studies without Biomarkers

Domain	Metric	Range of Metric Scores	Metric weighting Factor	Domain Weight	Range of Weighted Metric Scores
Study Participation	Participant Selection	1 to 3	0.4	1	0.4 to 1.2
	Attrition		0.4		0.4 to 1.2
	Comparison Group		0.2		0.2 to 0.6
Exposure Characterization	Measurement of Exposure		0.4	1	0.4 to 1.2
	Exposure Levels		0.2		0.2 to 0.6
	Temporality		0.4		0.4 to 1.2
Outcome Assessment	Outcome measurement or characterization		0.67	1	0.67 to 2.01
	Reporting Bias		0.33		0.33 to 0.99
Potential Confounding/ Variable Control	Covariate Adjustment		0.5	1	0.5 to 1.5
	Covariate Characterization		0.25		0.25 to 0.75
	Co-exposure Confounding/Moderation/Mediation		0.25		0.25 to 0.75
Analysis	Study Design and Methods		0.4	1	0.4 to 1.2
	Statistical Power		0.2		0.2 to 0.6
	Reproducibility of Analyses		0.2		0.2 to 0.6
	Statistical Models		0.2		0.2 to 0.6
Equation: Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor				*Sum of Weighted Scores = 5 to 15* Sum of Metric Weighting Factors= 5 5/5=1; 15/5=3	

Table H-7. Example of Scoring for Epidemiologic Studies where Sample Size is Not Applicable

Domain	Metric	Metric Score	Metric Weighting Factor	Weighted Score
Study Participation	1. Participant Selection	1	0.4	0.4
	2. Attrition	3	0.4	1.2
	3. Comparison Group	2	0.2	0.4
Exposure Characterization	4. Measurement of Exposure	1	0.4	0.4
	5. Exposure Levels	1	0.2	0.2
	6. Temporality	1	0.4	0.8
Outcome Assessment	7. Outcome measurement or characterization	3	0.67	2.01
	8. Reporting Bias	2	0.33	0.33
Potential Confounding/ Variable Control	9. Covariate Adjustment	1	0.67	0.67
	10. Covariate Characterization	1	0.33	0.33
	11. Co-exposure Confounding/Moderation/Mediation	NR	NR	NR
Analysis	12. Study Design and Methods	1	0.4	1.2
	13. Statistical Power	1	0.2	0.4
	14. Reproducibility of Analyses	3	0.2	0.2
	15. Statistical Models	3	0.2	0.6
		Sum of scores	5	8.47
		Overall Study Score	**1.7 = Medium**	

NR= not rated/not applicable

Equation:

Overall Score = Sum of Weighted Scores/Sum of Metric Weighting Factor

High	Medium	Low
≥1 and <1.7	≥1.7 and <2.3	≥2.3 and ≤3

H.5 Data Quality Criteria

Table H-8. Serious Flaws that Would Make Epidemiological Studies Unacceptable for Use in the Hazard Assessment

Optimization of the list of serious flaws may occur after pilot calibration exercises.

Domain	Metric	Description of Serious Flaw(s) in Data Source
Study Participation	Participant Selection	For all study types: The reported information indicates that selection in or out of the study (or analysis sample) and participation was likely to be significantly biased (i.e., the exposure-outcome distribution of the participants is likely not representative of the exposure-outcome distributions in the overall population of eligible persons.)
	Attrition	For cohort studies: The loss of subjects (i.e., incomplete outcome data) was large and unacceptably handled (as described above in the low confidence category) (Source: OHAT). OR Numbers of individuals were not reported at important stages of study (e.g., numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage [STROBE Checklist Item 13 (Von Elm et al., 2008)].
		For case-control and cross-sectional studies: The exclusion of subjects from analyses was large and unacceptably handled (as described above in the low confidence category). OR Reasons were not provided for non-participation at each stage [STROBE Checklist Item 13 (Von Elm et al., 2008)].
	Comparison Group	For cohort studies: Subjects in all exposure groups were not similar, recruited within very different time frames, or had the very different participation/ response rates (NTP, 2015a). OR Information was not reported to determine if participants in all exposure groups were similar [STROBE Checklist 6 (Von Elm et al., 2008)]
		For case-control studies: Controls were drawn from a very dissimilar population than cases or recruited within very different time frames (NTP, 2015a). OR Rationale and/or methods for case and control selection, matching criteria including number of controls per case (if relevant) were not reported [STROBE Checklist 6 (Von Elm et al., 2008)].
		For cross-sectional studies: Subjects in all exposure groups were not similar, recruited within very different time frames, or had the very different participation/response rates (NTP, 2015a).

		OR Sources and methods of selection of participants in all exposure groups were not reported [STROBE Checklist 6 (Von Elm et al., 2008)].
Exposure Characterization	Measurement of Exposure	For all study types: Exposure variables were not well defined, and sources of data and detailed methods of exposure assessment were not reported [STROBE Checklist 7 and 8 (Von Elm et al., 2008)]. OR Exposure was assessed using methods known or suspected to have poor validity (Source: OHAT). OR There is evidence of substantial exposure misclassification that would significantly alter results.
	Exposure Levels	For all study types: The levels of exposure are not sufficient or adequate (as defined above) to detect an effect of exposure (Cooper et al., 2016). OR No description is provided on the levels or range of exposure.
	Temporality	For all study types: Study lacks an established time order, such that exposure is not likely to have occurred prior to outcome (Lakind et al., 2014). OR Exposures clearly fell outside of relevant exposure window for the outcome of interest. OR For each variable of interest (outcome and predictor), sources of data and details of methods of assessment were not reported (e.g., periods of exposure, dates of outcome ascertainment, etc.) [STROBE Checklist 8 (Von Elm et al., 2008)].
Outcome Assessment	Outcome measurement or characterization	For all study types: Numbers of outcome events or summary measures, or diagnostic criteria were not defined or reported [STROBE Checklist 15 (Von Elm et al., 2008)].
Potential Confounding/Variable Control	Covariate adjustment	For cohort and cross-sectional studies: The distribution of primary covariates (excluding co-exposures) and known confounders differed significantly between the exposure groups OR Confounding was demonstrated and was not appropriately adjusted for in the final analyses (NTP, 2015a).
		For case-control studies: The distribution of primary covariates (excluding co-exposures) and known confounders differed significantly between cases and controls. OR Confounding was demonstrated and was not appropriately adjusted for in the final analyses (NTP, 2015a).
	Covariate characterization	For all study types: Primary covariates (excluding co-exposures) and confounders were not assessed.

	Co-exposure Confounding/ Moderation/ Mediation	For cohort and cross-sectional studies: There is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for.
		For case-control studies: There is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for, and significant indication a biased exposure-outcome association.
Analysis	Study design and methods	For all study types: The study design chosen was not appropriate for the research question. OR Inappropriate statistical analyses were applied to assess the research questions.
	Statistical power (sensitivity)	For cohort and cross-sectional studies: The number of participants are inadequate to detect an effect in the exposed population and/or subgroups of the total population.
		For case-control studies: The number of cases and controls are inadequate to detect an effect in the exposed population and/or subgroups of the total population.
Other (if applicable) Considerations for Biomarker Selection and Measurement (Lakind et al., 2014)	Use of Biomarker of Exposure	Biomarker in a specified matrix is a poor surrogate (low accuracy and precision) for exposure/dose.
	Effect biomarker	Biomarker has undetermined consequences (e.g., biomarker is not specific to a health outcome).
	Method sensitivity	Frequency of detection too low to address the research hypothesis. OR LOD/LOQ (value or %) are not stated.
	Biomarker stability	Samples with either unknown storage history and/or no stability data for target analytes and high likelihood of instability for the biomarker under consideration.
	Sample contamination	There are known contamination issues and no documentation that the issues were addressed.
	Method requirements	Instrumentation that only allows for possible quantification of the biomarker, but the method has known interferants (e.g., GC–FID, spectroscopy).
	Matrix adjustment	If applicable for the biomarker under consideration, no established method for matrix adjustment was conducted.

Table H-9. Evaluation Criteria for Epidemiological Studies

Confidence Level (Score)	Description	Selected Score
Domain 1. Study Participation		
Metric 1. Participant selection (selection, performance biases)		
Instructions: To meet criteria for confidence ratings for metrics where 'AND' is included, studies must address both of the conditions where "AND" is stipulated. To meet criteria for confidence ratings for metrics where 'OR' is included studies must address at least one of the conditions stipulated.		
High (score = 1)	• ***For all study types:*** All key elements of the study design are reported (i.e., setting, participation rate described at all steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) **AND** The reported information indicates that selection in or out of the study (or analysis sample) and participation was not likely to be biased (i.e., the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the overall population of eligible persons.)	
Medium (score = 2)	• ***For all study types:*** Some key elements of the study design were not present but available information indicates a low risk of selection bias (i.e., the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the overall population of eligible persons.)	
Low (score = 3)	• ***For all study types:*** Key elements of the study design and information on the comparison group (i.e., setting, participation rate described at most steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) are not reported [STROBE checklist 4, 5 and 6 (Von Elm et al., 2008)].	
Unacceptable (score = 4)	• ***For all study types:*** The reported information indicates that selection in or out of the study (or analysis sample) and participation was likely to be significantly biased (i.e., the exposure-outcome distribution of the participants are likely not representative of the exposure-outcome distributions in the overall population of eligible persons.)	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 2. Attrition (missing data/attrition/exclusion, reporting biases)		
High (score = 1)	• ***For cohort studies:*** There was minimal subject attrition during the study (or exclusion from the analysis sample) and outcome data were largely complete. **OR** • Any loss of subjects (i.e., incomplete outcome data) was adequately* addressed (as described above) and reasons were documented when human subjects were removed from a study (NTP, 2015a). **OR** • Missing data have been imputed using appropriate methods (e.g., random regression imputation), and characteristics of subjects lost to follow up or with unavailable records are described in identical way and are not significantly different from those of the study participants (NTP, 2015a).	

	• ***For case-control studies and cross-sectional studies:*** There was minimal subject withdrawal from the study (or exclusion from the analysis sample) and outcome data were largely complete. **OR** • Any exclusion of subjects from analyses was adequately* addressed (as described above), and reasons were documented when subjects were removed from the study or excluded from analyses (NTP, 2015a). ***NOTE for all study types:*** Adequate handling of subject attrition includes: very little missing outcome data; reasons for missing subjects unlikely to be related to outcome (for survival data, censoring was unlikely to introduce bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups.	
Medium (score = 2)	• ***For cohort studies:*** There was moderate subject attrition during the study (or exclusion from the analysis sample). **AND** • Any loss or exclusion of subjects was adequately addressed (as described in the acceptable handling of subject attrition in the high confidence category) and reasons were documented when human subjects were removed from a study. • ***For case-control studies and cross-sectional studies:*** There was moderate subject withdrawal from the study (or exclusion from the analysis sample), but outcome data were largely complete. **AND** • Any exclusion of subjects from analyses was adequately addressed (as described above), and reasons were documented when subjects were removed from the study or excluded from analyses (NTP, 2015a).	
Low (score = 3)	• ***For cohort studies:*** There was large subject attrition during the study (or exclusion from the analysis sample). **OR** • Unacceptable handling of subject attrition: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation (Source: OHAT). • ***For case-control and cross-sectional studies:*** There was large subject withdrawal from the study (or exclusion from the analysis sample). **OR** • Unacceptable handling of subject attrition: reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across study groups; or potentially inappropriate application of imputation.	
Unacceptable (score = 4)	• ***For cohort studies:*** The loss of subjects (i.e., incomplete outcome data) was large and unacceptably handled (as described above in the low confidence category) (Source: OHAT). **OR** • Numbers of individuals were not reported at important stages of study (e.g., numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage [STROBE Checklist Item 13 (Von Elm et al., 2008)]. • ***For case-control and cross-sectional studies:*** The exclusion of subjects from analyses was large and unacceptably handled (as described above in the low confidence category).	

	OR • Reasons were not provided for non-participation at each stage [STROBE Checklist Item 13 (Von Elm et al., 2008)].	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 3. Comparison Group (selection, performance biases)		
High (score = 1)	• ***For cohort and cross-sectional studies:*** Key elements of the study design are reported (i.e., setting, inclusion and exclusion criteria, and methods of participant selection), and indicate that subjects (in all exposure groups) were similar (e.g., recruited from the same eligible population with the same method of ascertainment and within the same time frame using the same inclusion and exclusion criteria, and were of similar age and health status) (NTP, 2015a). • ***For case-control studies:*** Key elements of the study design are reported (i.e., setting, inclusion and exclusion criteria, and methods of case ascertainment or control selection), and indicate that that cases and controls were similar (e.g., recruited from the same eligible population with appropriate matching criteria, such as age, gender, and ethnicity, the number of controls described, and eligibility criteria other than outcome of interest as appropriate), recruited within the same time frame, and controls are described as having no history of the outcome (NTP, 2015a). **OR** • ***For all study types:*** Baseline characteristics of groups differed ***but*** these differences were considered as potential confounding or stratification variables, and were thereby controlled by statistical analysis (Source: OHAT).	
Medium (score = 2)	• ***For cohort studies:*** There is indirect evidence (e.g., stated by the authors without providing a description of methods) that subjects (in all exposure groups) are similar (as described above for the high confidence rating). **AND** • The baseline characteristics for subjects (in all exposure groups) reported in the study are similar (NTP, 2015a). • ***For case-control studies***: There is indirect evidence (i.e., stated by the authors without providing a description of methods) that that cases and controls are similar (as described above for the high confidence rating). **AND** • The characteristics of case and controls reported in the study are similar (NTP, 2015a). • ***For cross-sectional studies:*** There is indirect evidence (i.e., stated by the authors without providing a description of methods) that subjects (in all exposure groups) are similar (as described above for the high confidence rating) (Source: OHAT). **AND** • The characteristics of participants (in all exposure groups) reported in the study are similar.	
Low (score = 3)	• ***For cohort studies***: There is indirect evidence (i.e., stated by the authors without providing a description of methods) that subjects (in all exposure groups) were similar (as described above for the high confidence rating).	

	AND • The baseline characteristics for subjects (in all exposure groups) are not reported (NTP, 2015a). • ***For case-control studies***: There is indirect evidence (i.e., stated by the authors without providing a description of methods) that that cases and controls were similar (as described above for the high confidence rating). **AND** • The characteristics of case and controls are not reported (Source: (NTP, 2015a). • ***For cross-sectional studies:*** There is indirect evidence (i.e., stated by the authors without providing a description of method) that subjects (in all exposure groups) were similar (as described above for the high confidence rating). **AND** • The characteristics of participants (in all exposure groups) are not reported (Source: OHAT).	
Unacceptable (score = 4)	• ***For cohort studies:*** Subjects in all exposure groups were not similar, recruited within very different time frames, or had the very different participation/ response rates (NTP, 2015a). **OR** • Information was not reported to determine if participants in all exposure groups were similar [STROBE Checklist 6 (Von Elm et al., 2008)] • ***For case-control studies:*** Controls were drawn from a very dissimilar population than cases or recruited within very different time frames (NTP, 2015a). **OR** • Rationale and/or methods for case and control selection, matching criteria including number of controls per case (if relevant) were not reported [STROBE Checklist 6 (Von Elm et al., 2008)]. • ***For cross-sectional studies:*** Subjects in all exposure groups were not similar, recruited within very different time frames, or had the very different participation/response rates (NTP, 2015a). **OR** • Sources and methods of selection of participants in all exposure groups were not reported [STROBE Checklist 6 (Von Elm et al., 2008)].	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 2. Exposure Characterization		
Metric 4. Measurement of Exposure (Detection/measurement/information, performance biases)		
High (score = 1)	• ***For all study types:*** Exposure was consistently assessed (i.e., under the same method and time-frame) using well-established methods (e.g., personal and/or industrial hygiene data used to determine levels of exposure, a frequently used biomarker of exposure) that directly measure exposure (e.g., measurement of the chemical in the environment (air, drinking water, consumer product, etc.) or measurement of the chemical concentration in a biological matrix such as blood, plasma, urine, etc.) (NTP, 2015a).	
Medium (score = 2)	• ***For all study types:*** Exposure was directly measured and assessed using a method that is not well-established (e.g., newly developed biomarker of exposure), ***but*** is validated against a well-established method and demonstrated a high agreement between the two methods.	

Low (score = 3)	• ***For all study types:*** A less-established method (e.g., newly developed biomarker of exposure) was used and no method validation was conducted against well-established methods, but there was little to no evidence that the method had poor validity and little to no evidence of significant exposure misclassification (e.g., differential recall of self-reported exposure) (Source: OHAT).	
Unacceptable (score = 4)	• ***For all study types:*** Exposure variables were not well defined, and sources of data and detailed methods of exposure assessment were not reported [STROBE Checklist 7 and 8 (Von Elm et al., 2008)]. **OR** • Exposure was assessed using methods known or suspected to have poor validity (Source: OHAT). **OR** • There is evidence of substantial exposure misclassification that would significantly alter results.	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 5. Exposure levels (Detection/measurement/information biases)		
High (score = 1)	• ***For all study types:*** The levels of exposure are sufficient* or adequate to detect an effect of exposure {Cooper, 2016, 3121908}. * Sufficient or adequate for cohort and cross-sectional studies includes the reporting of at least 2 levels of exposure (referent group + 1 or more exposure groups) (Cooper) that capture exposure spatial and temporal variability within the study population (Source: IRIS).	
Medium (score = 2)	• Do not select for this metric.	
Low (score = 3)	• Do not select for this metric.	
Unacceptable (score = 4)	• ***For all study types:*** The levels of exposure are not sufficient or adequate (as defined above) to detect an effect of exposure (Cooper et al., 2016). **OR** • No description is provided on the levels or range of exposure.	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 6. Temporality (Detection/measurement/information biases)		
High (score = 1)	• ***For all study types:*** The study presents an established time order between exposure and outcome. **AND** • The interval between the exposure (or reconstructed exposure) and the outcome has an appropriate consideration of relevant exposure windows (Lakind et al., 2014).	
Medium	• ***For all study types:*** Temporality is established, but it is unclear whether	

(score = 2)	• exposures fall within relevant exposure windows for the outcome of interest (Lakind et al., 2014).	
Low (score = 3)	• ***For all study types:*** The temporality of exposure and outcome is uncertain.	
Unacceptable (score = 4)	• ***For all study types:*** Study lacks an established time order, such that exposure is not likely to have occurred prior to outcome (Lakind et al., 2014). **OR** • Exposures clearly fell outside of relevant exposure window for the outcome of interest. **OR** • For each variable of interest (outcome and predictor), sources of data and details of methods of assessment were not reported (e.g. periods of exposure, dates of outcome ascertainment, etc.) [STROBE Checklist 8 (Von Elm et al., 2008)].	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 3. Outcome Assessment		
Metric 7. Outcome measurement or characterization (detection/measurement/information, performance, reporting biases)		
High (score = 1)	• ***For cohort studies:*** The outcome was assessed using well-established methods (e.g., the "gold standard"). **AND** • Subjects had been followed for the same length of time in all study groups. • ***For case-control studies:*** The outcome was assessed in cases (i.e., case definition) and controls using well-established methods (the gold standard). **AND** • Subjects had been followed for the same length of time in all study groups (NTP, 2015a). ***For cross-sectional studies***: There is direct evidence that the outcome was assessed using well-established methods (the gold standard) (NTP, 2015a). *Note: Acceptable assessment methods will depend on the outcome, but examples of such methods may include: objectively measured with diagnostic methods, measured by trained interviewers, obtained from registries (NTP, 2015a; Shamliyan et al., 2010).	
Medium (score = 2)	• ***For all study types:*** A less-established method was used and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of outcome misclassification (e.g., differential reporting of outcome by exposure status).	
Low (score = 3)	• ***For cohort studies:*** The outcome assessment method is an insensitive instrument or measure. **OR** • The length of follow up differed by study group (NTP, 2015a). • ***For case-control studies:*** The outcome was assessed in cases (i.e., case definition) using an insensitive instrument or measure (NTP, 2015a). • ***For cross-sectional studies:*** The outcome assessment method is an insensitive instrument or measure (NTP, 2015a).	

Unacceptable (score = 4)	• ***For all study types:*** Numbers of outcome events or summary measures, or diagnostic criteria were not defined or reported [STROBE Checklist 15 (Von Elm et al., 2008)].	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 8. Reporting Bias		
High (score = 1)	• ***For all study types:*** All of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) are reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction and analyses had been planned in advance (NTP, 2015a).	
Medium (score = 2)	• ***For all study types:*** All of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) are reported, but not in a way that would allow for detailed extraction (e.g., results were discussed in the text but accompanying data were not shown).	
Low (score = 3)	• ***For all study types:*** All of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified or reporting outcomes not pre-specified, or that unplanned analyses were included that would appreciably bias results (NTP, 2015a).	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 4. Potential Confounding/Variable Control		
Metric 9. Covariate Adjustment (confounding)		
High (score = 1)	• ***For all study types:*** Appropriate adjustments or explicit considerations were made for primary covariates (excluding co-exposures) and confounders in the final analyses through the use of statistical models to reduce research-specific bias, including standardization, matching, adjustment in multivariate models, stratification, or other methods that were appropriately justified (NTP, 2015a).	
Medium (score = 2)	• ***For all study types:*** There is indirect evidence that appropriate adjustments were made (i.e., considerations were made for primary covariates (excluding co-exposures) and confounders adjustments) without providing a description of methods. **OR** • The distribution of primary covariates (excluding co-exposures) and known confounders did not differ significantly between exposure groups or between cases and controls.	

	OR • The majority of the primary covariates (excluding co-exposures) and any known confounders were appropriately adjusted and any not adjusted for are considered not to appreciably bias the results.	
Low (score = 3)	• ***For all study types:*** There is indirect evidence (i.e., no description is provided in the study) that considerations were not made for primary covariates (excluding co-exposures) and confounders adjustments in the final analyses (NTP, 2015a). **AND** • The distribution of primary covariates (excluding co-exposures) and known confounders was not reported between the exposure groups or between cases and controls (NTP, 2015a).	
Unacceptable (score = 4)	• ***For cohort and cross-sectional studies:*** The distribution of primary covariates (excluding co-exposures) and known confounders differed significantly between the exposure groups **OR** • Confounding was demonstrated and was not appropriately adjusted for in the final analyses (NTP, 2015a). • ***For case-control studies:*** The distribution of primary covariates (excluding co-exposures) and known confounders differed significantly between cases and controls. **OR** • Confounding was demonstrated and was not appropriately adjusted for in the final analyses (NTP, 2015a).	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 10. Covariate Characterization (measurement/information, confounding biases)		
High (score = 1)	• ***For all study types:*** Primary covariates (excluding co-exposures) and confounders were assessed using valid and reliable methodology (e.g., validated questionnaires, biomarker).	
Medium (score = 2)	• ***For all study types:*** A less-established method was used and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of confounding.	
Low (score = 3)	• ***For all study types:*** The primary covariate (excluding co-exposures) and confounder assessment method is an insensitive instrument or measure or a method of unknown validity.	
Unacceptable (score = 4)	• ***For all study types:*** Primary covariates (excluding co-exposures) and confounders were not assessed.	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Metric 11. Co-exposure Confounding/Moderation/Mediation (measurement/information, confounding biases)		
High (score = 1)	• ***For all study types:*** Any co-exposures to pollutants that are not the target exposure that would likely bias the results were not present. **OR** • Co-exposures to pollutants were appropriately measured and adjusted for.	
Medium (score = 2)	• Do not select for this metric.	
Low (score = 3)	• Do not select for this metric.	
Unacceptable (score = 4)	• ***For cohort and cross-sectional studies:*** There is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for. • ***For case-control studies:*** There is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for, and significant indication a biased exposure-outcome association.	
Not rated/applicable	• Enter 'NA' and do not score this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 5. Analysis		
Metric 12. Study Design and Methods (reporting bias)		
High (score = 1)	• ***For all study types:*** The study design chosen was appropriate for the research question (e.g. assess the association between exposure levels and common chronic diseases over time with cohort studies, assess the association between exposure and rare diseases with case-control studies, and assess the association between exposure levels and acute disease with a cross-sectional study design). **AND** • The study uses an appropriate statistical method to address the research question(s) (e.g., repeated measures analysis for longitudinal studies, logistic regression analysis for case-control studies).	
Medium (score = 2)	• Do not select for this metric.	
Low (score = 3)	• Do not select for this metric.	
Unacceptable (score = 4)	***For all study types:*** The study design chosen was not appropriate for the research question. **OR** • Inappropriate statistical analyses were applied to assess the research questions.	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 13. Statistical power (sensitivity, reporting bias)		
High (score = 1)	• ***For cohort and cross-sectional studies:*** The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population.	

	OR • The paper reported statistical power high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population. • ***For case-control studies:*** The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** • The paper reported statistical power was high (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population.	
Medium (score = 2)	• Do not select for this metric.	
Low (score = 3)	• Do not select for this metric.	
Unacceptable (score = 4)	• ***For cohort and cross-sectional studies:*** The number of participants are inadequate to detect an effect in the exposed population and/or subgroups of the total population. • ***For case-control studies:*** The number of cases and controls are inadequate to detect an effect in the exposed population and/or subgroups of the total population.	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 14. Reproducibility of analyses [adapted from Blettner et al. (2001)]		
High (score = 1)	• ***For all study types:*** The description of the analysis is sufficient to understand precisely what has been done and to be reproducible.	
Medium (score = 2)	• Do not select for this metric.	
Low (score = 3)	• ***For all study types:*** The description of the analysis is insufficient to understand what has been done and to be reproducible OR a description of analyses are not present (e.g., statistical tests and estimation procedures were not described, variables used in the analysis were not listed, transformations of continuous variables (such as logarithm) were not explained, rules for categorization of continuous variables were not presented, deleting of outliers were not elucidated and how missing values are dealt with was not mentioned).	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/applicable	• Do not select for this metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 15. Statistical Models (confounding bias)		
High (score = 1)	• ***For all study types:*** The statistical model building process is transparent (it is stated how/why variables were included or excluded from the multivariate model) AND model assumptions were met.	
Medium (score = 2)	• Do not select for this metric.	

Low (score = 3)	• ***For all study types:*** The statistical model building process is not transparent OR it is not stated how/why variables were included or excluded from the multivariate model OR model assumptions were not met OR a description of analyses are not present OR no sensitivity analyses are described OR model assumptions were not discussed [STROBE Checklist 12e (Von Elm et al., 2008)].	
Unacceptable (score = 4)	• Do not select for this metric.	
Not rated/applicable	• Enter 'NA' if the study did not use a statistical model.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Domain 6. Other (if applicable) Considerations for Biomarker Selection and Measurement Lakind et al. (2014)		
Metric 16. Use of Biomarker of Exposure (detection/measurement/information biases)		
High (score = 1)	• Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. **AND** • Biomarker is derived from exposure to one parent chemical.	
Medium (score = 2)	• Biomarker in a specified matrix has accurate and precise quantitative relationship with external exposure, internal dose, or target dose. **AND** • Biomarker is derived from multiple parent chemicals.	
Low (score = 3)	• Evidence exists for a relationship between biomarker in a specified matrix and external exposure, internal dose or target dose, but there has been no assessment of accuracy and precision or none was reported.	
Unacceptable (score = 4)	• Biomarker in a specified matrix is a poor surrogate (low accuracy and precision) for exposure/dose.	
Not rated/applicable	• Enter 'NA' and do not score the metric if no biomarker of exposure was measured.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 17. Effect biomarker (detection/measurement/information biases)		
High (score = 1)	• Bioindicator of a key event in an AOP.	
Medium (score = 2)	• Biomarkers of effect shown to have a relationship to health outcomes using well validated methods, but the mechanism of action is not understood.	
Low (score = 3)	• Biomarkers of effect shown to have a relationship to health outcomes, but the method is not well validated and mechanism of action is not understood.	
Unacceptable (score = 4)	• Biomarker has undetermined consequences (e.g., biomarker is not specific to a health outcome).	
Not rated/applicable	• Enter 'NA' and do not score the metric if no biomarker of effect was measured.	
Reviewer's comments		
Metric 18. Method sensitivity (detection/measurement/information biases)		
High (score = 1)	• Limits of detection are low enough to detect chemicals in a sufficient percentage of the samples to address the research question.	
Medium (score = 2)	• Do not select for this metric.	

Low (score = 3)	• Do not select for this metric.	
Unacceptable (score = 4)	• Frequency of detection too low to address the research hypothesis. **OR** • LOD/LOQ (value or %) are not stated.	
Not rated/applicable	• Enter 'NA' and do not score the metric.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 19. Biomarker stability (detection/measurement/information biases)		
High (score = 1)	• Samples with a known history and documented stability data or those using real-time measurements.	
Medium (score = 2)	• Do not select for this metric.	
Low (score = 3)	• Samples have known losses during storage, but the difference between low and high exposures can be qualitatively assessed.	
Unacceptable (score = 4)	• Samples with either unknown storage history and/or no stability data for target analytes and high likelihood of instability for the biomarker under consideration. •	
Not rated/applicable	• Enter 'NA' and do not score the metric if no biomarkers were assessed.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 20. Sample contamination (detection/measurement/information biases)		
High (score = 1)	• Samples are contamination-free from the time of collection to the time of measurement (e.g., by use of certified analyte free collection supplies and reference materials, and appropriate use of blanks both in the field and lab). **AND** • Documentation of the steps taken to provide the necessary assurance that the study data are reliable is included.	
Medium (score = 2)	• Samples are stated to be contamination-free from the time of collection to the time of measurement. **AND** • There is incomplete documentation of the steps taken to provide the necessary assurance that the study data are reliable.	
Low (score = 3)	• Samples are known to have contamination issues, but steps have been taken to address and correct contamination issues. **OR** • Samples are stated to be contamination-free from the time of collection to the time of measurement, but there is no use or documentation of the steps taken to provide the necessary assurance that the study data are reliable.	
Unacceptable (4)	• There are known contamination issues and no documentation that the issues were addressed.	
Not rated/applicable	• Enter 'NA' and do not score the metric if no samples were collected.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

Metric 21. Method requirements (detection/measurement/information biases)		
High (score = 1)	• Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity (e.g., GC–HRMS, GC–MS/MS, LC–MS/MS).	
Medium (score = 2)	• Do not select for this metric.	
Low (score = 3)	• Instrumentation that allows for identification of the biomarker with a high degree of confidence and the required sensitivity (e.g., GC–MS, GC–ECD).	
Unacceptable (score = 4)	• Instrumentation that only allows for possible quantification of the biomarker, but the method has known interferants (e.g., GC–FID, spectroscopy).	
Not rated/applicable	• Enter 'NA' and do not score the metric if biomarkers were not measured.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	
Metric 22. Matrix adjustment (detection/measurement/information biases)		
High (score = 1)	• If applicable for the biomarker under consideration, study provides results, either in the main publication or as a supplement, for adjusted and unadjusted matrix concentrations (e.g., creatinine-adjusted or SG-adjusted and non-adjusted urine concentrations) and reasons are given for adjustment approach.	
Medium (score = 2)	• Do not select for this metric.	
Low (score = 3)	• If applicable for the biomarker under consideration, study only provides results using one method (matrix-adjusted or not).	
Unacceptable (score = 4)	• If applicable for the biomarker under consideration, no established method for matrix adjustment was conducted.	
Not rated/applicable	• Enter 'NA' and do not score the metric if not applicable for the biomarker or no biomarker was assessed.	
Reviewer's comments	*[Document concerns, uncertainties, limitations, and deficiencies and any additional comments that may highlight study strengths or important elements such as relevance]*	

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Environmental Defense Fund Comments on

Ten Problem Formulations under the Toxic Substances Control Act

Docket IDs: EPA-HQ-OPPT-2018-0210 (Problem Formulations for Risk Evaluations To Be Conducted Under Toxic Substances Control Act, and General Guiding Principles To Apply Systematic Review in TSCA Risk Evaluations), EPA-HQ-OPPT-2016-0723 (1-4, Dioxane), EPA-HQ-OPPT-2016-0725 (Pigment Violet 29), EPA-HQ-OPPT-2016-0732 (Tetrachloroethylene), EPA-HQ-OPPT-2016-0733 (Carbon Tetrachloride), EPA-HQ-OPPT-2016-0735 (HBCD), EPA-HQ-OPPT-2016-0736 (Asbestos), EPA-HQ-OPPT-2016-0737 (Trichloroethylene), EPA-HQ-OPPT-2016-0741 (1-Bromopropane), EPA-HQ-OPPT-2016-0742 (Methylene Chloride), and EPA-HQ-OPPT-2016-0743 (N-Methylpyrrolidone)

Submitted Thursday, August 16, 2018

Environmental Defense Fund (EDF) appreciates the opportunity to provide comments to the Environmental Protection Agency (EPA) on the problem formulations for the risk evaluations for the first ten chemicals being evaluated under section 6(b)(4) of the Toxic Substances Control Act (TSCA) as amended by the Lautenberg Act, enacted on June 22, 2016.

EDF is first providing comments addressing all of the problem formulations for the first 10 chemicals. While our comments are broadly applicable to all of the problem formulation documents, we include examples from specific documents to illustrate flaws and limitations. Later in these comments, we provide more detailed comments on each chemical-specific problem formulations. It should be noted that many of the issues identified in these chemical-specific comments are also applicable to other problem formulations. EDF requests that EPA consider all of these comments as they apply to each problem formulation.

EDF previously provided comments on the scopes for these ten chemicals. In those comments, EDF identified a variety of legal violations and other problems with EPA's approach to these risk evaluations. Unfortunately, those same violations and problems appear in the problem formulations, along with new ones. EDF incorporates and reiterates those points here as well.[1] Similarly, EDF has, as part of a broader coalition, filed a Brief explaining why the Risk Evaluation Rule is illegal and arbitrary and capricious. For these same reasons, it is illegal and arbitrary and capricious for EPA to follow the Rule in developing

[1] EDF Comments on Ten Scopes under the Toxic Substances Control Act, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069.

these risk evaluations. EDF incorporates and reiterates those points here as well. We attach that Brief as Appendix A. EPA should fix all of these problems in its draft risk evaluations.

The following short citations will be used throughout EDF's comment to refer to each of the ten problem formulations:

- U.S. EPA, Problem Formulation of the Risk Evaluation for Asbestos (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0736-0131 (hereinafter "Problem Formulation for Asbestos").
- U.S. EPA, Problem Formulation of the Risk Evaluation for 1-Bromopropane (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0741-0067 (hereinafter "Problem Formulation for 1-BP").
- U.S. EPA, Problem Formulation of the Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-) CASRN: 56-23-5 (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0733-0068 (hereinafter "Problem Formulation for Carbon Tetrachloride").
- U.S. EPA, Problem Formulation for Cyclic Aliphatic Bromides Cluster (HBCD) (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0735-0071 (hereinafter "Problem Formulation for HBCD").
- U.S. EPA, Problem Formulation of the Risk Evaluation for 1,4-Dioxane (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0723-0064 (hereinafter "Problem Formulation for 1,4-Dioxane").
- U.S. EPA, Problem Formulation of the Risk Evaluation for Methylene Chloride (Dichloromethane, DCM) (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0742-0083 (hereinafter "Problem Formulation for DCM").
- U.S. EPA, Problem Formulation of the Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0076 (hereinafter "Problem Formulation for NMP").
- U.S. EPA, Problem Formulation of the Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro) (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0732-0080 (hereinafter "Problem Formulation for Perchloroethylene").
- U.S. EPA, Problem Formulation of the Risk Evaluation for Trichloroethylene (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0737-0083 (hereinafter "Problem Formulation for TCE").
- U.S. EPA, Problem Formulation of the Risk Evaluation for C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f']diisoquinoline- 1,3,8,10(2H,9H)-tetrone) (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0725-0048 (hereinafter "Problem Formulation for PV 29").

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COMMENTS APPLICABLE TO ALL TEN PROBLEM FORMULATIONS

1. TSCA requires EPA to analyze whether a chemical substance, as a whole, presents an unreasonable risk, and EPA does not have discretion to ignore conditions of use, exposures, or hazards.

In its prior scoping documents, EPA stated that it had authority to exclude conditions of use. In our comments on those documents, EDF explained that this approach is foreclosed under the statute, and EDF incorporates those arguments here.[2] Similarly, EDF incorporates the arguments presented in our Brief attached as Appendix A at 21-40.

In the problem formulations, EPA states that it will also exclude hazards and exposures under the condition of use as well. TSCA's language and structure unambiguously foreclose EPA's interpretation. EPA's decision to disregard certain exposure pathways and hazards is also "arbitrary, capricious, [or] an abuse of discretion" under the APA, 5 U.S.C. § 706(2)(A), because it will lead EPA to consider "factors which Congress has not intended it to consider [and] entirely fail[] to consider an important aspect of the problem." *Motor Vehicle Mfrs. Ass'n v. State Farm Mut. Auto. Ins. Co.*, 463 U.S. 29, 43 (1983). Moreover, as the problem formulations themselves reveal, this approach leads to irrational and arbitrary applications. Instead, EPA should be guided by the statutory language and consider all of the conditions of use, exposures, and hazards related to a chemical substance. EPA should evaluate all of the evidence of conditions of use, exposure, and hazard; not ignore evidence because of self-imposed blinders.

A. The plain text, overall structure, purpose, and legislative history of TSCA indicate that EPA has to determine whether a chemical substance presents an unreasonable risk comprehensively, considering all of its hazards, exposures, and conditions of use.

i) The plain text requires EPA to consider all hazards, exposures, and conditions of use.

Statutory interpretation should begin, as always, with the language of the statute. The plain language of the risk evaluation provision supports the interpretation that EPA must consider all hazards, exposures, and conditions of use as necessary "to determine whether a *chemical substance* presents an unreasonable risk." 15 U.S.C. § 2605(b)(4)(A) (emphasis added). This directive expresses Congress's clear intent that EPA evaluate the risks posed by "a chemical substance" as a whole. Congress consistently used the phrase "a chemical substance" to describe the object of priority designations and risk evaluations. 15 U.S.C. § 2605(b)(1)-(4), (i) (using the phrase 14 times). This language requires EPA to consider all hazards and exposures that contribute to the total risk presented by the chemical substance as a whole.

This whole-substance focus begins during prioritization. The definitions of high- and low-priority substances make clear that it is the "substance" that receives the designation, not selected conditions of

[2] EDF Comments on Ten Scopes under the Toxic Substances Control Act, pp. 4-11, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069.

use, exposures, or hazards. *See id.* § 2605(b)(1)(B). The provision requiring EPA to select the first ten chemicals also directed that the risk evaluations be "conducted on 10 chemical substances drawn from the 2014 update of the TSCA Work Plan," making the object of these risk evaluations the chemical substances as a whole. *Id.* § 2605(b)(2)(A). As EPA reasoned in the Prioritization Rule, "[t]he statute is clear that EPA is to designate the priority of the 'chemical substance'—not a condition of use for a chemical substance." 82 Fed. Reg. 33,753, 33,755 (July 20, 2017) (citing 15 U.S.C. § 2605(b)(1)(A)). Similarly, EPA must prioritize the whole chemical, and EPA is not directed to prioritize only certain hazards or exposures. Indeed, the prioritization process expressly "shall include a consideration of the hazard and exposure potential of a chemical substance," without any basis for EPA to limit that consideration to only certain hazards or exposures. 15 U.S.C. § 2605(b)(1)(A).

EPA must also conduct risk evaluations on "a chemical substance" as a whole. For example, TSCA provides that "[u]pon designating a chemical substance as a high-priority substance, the Administrator shall initiate a risk evaluation on the *substance*." 15 U.S.C. § 2605(b)(3)(A) (emphasis added). Similarly, the statute directs EPA to determine either that "a *chemical substance* presents" or "does not present an unreasonable risk." *Id.* § 2605(i)(1)-(2) (emphasis added). Congress also uses the phrase "a chemical substance" or "chemical substances" in many other places in TSCA's risk evaluation provisions. *See, e.g.*, *id.* § 2605(b)(4)(G) (setting deadlines for completing evaluation for "a chemical substance"), (b)(2)(A), (b)(2)(B), (b)(3)(A), (c)(1).

The plain language of the risk evaluation provisions requires EPA to consider all available information about hazards, exposures, and conditions of use, without limitation. TSCA § 6(b)(4)(F)(i) expressly requires that EPA "integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance." 15 U.S.C. § 2605(b)(4)(F)(i). Thus, if there is "available information on hazards and exposures," then EPA must integrate and assess that information as part of the risk evaluation. Similarly, TSCA § 6(b)(4)(F)(iv) requires that EPA "take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use of the chemical substance." *Id.* § 2605(b)(4)(F)(iv). This provision requires EPA to take into account exposures unless EPA can establish that they are irrelevant. Finally, TSCA § 6(b)(4)(F)(v) requires that EPA "describe the weight of the scientific evidence for the identified hazard and exposure." *Id.* § 2605(b)(4)(F)(v).

All of these provisions direct EPA to consider a chemical's hazards, exposures, and conditions of use, and none of them include any language providing EPA with any discretion to ignore any hazards, exposures, or conditions of use. While EPA previously articulated a legal theory (albeit flawed) for ignoring certain conditions of use, EPA has not pointed to any legal basis for ignoring hazards or exposures under the conditions of use being analyzed in a risk evaluation. EPA has pointed to no textual basis for these exclusions.

Moreover, when EPA promulgates risk-management regulations under TSCA § 6(a):

> [EPA] shall consider and publish a statement based on reasonably available information with respect to—

(i) the effects of the chemical substance or mixture on health and the magnitude of the exposure of human beings to the chemical substance or mixture;

(ii) the effects of the chemical substance or mixture on the environment and the magnitude of the exposure of the environment to such substance or mixture;

15 U.S.C. § 2605(c)(2)(A). In order to accurately draft this statement, EPA will have to have considered all of the hazards posed by a chemical (i.e., its effects on human health and the environment) as well as all exposures. EPA cannot accurately describe "the magnitude of the exposure of human beings to the chemical substance," if EPA has ignored numerous exposures. 15 U.S.C. § 2605(c)(2)(A)(i). Similarly, EPA cannot accurately describe "the magnitude of the exposure of the environment" for chemicals, *id.* § 2605(c)(2)(A)(ii), if EPA has ignored the vast majority of environmental exposures, as EPA proposes to do. Congress specifically intended for EPA to "satisfy these requirements on the basis of the conclusions regarding the chemical's health and environmental effects and exposures in the risk evaluation itself." 114 Cong. Rec. S3517 (daily ed. June 7, 2016). Thus, EPA must evaluate all hazards and exposures in its risk evaluations.

Moreover, TSCA requires that EPA evaluate a chemical's risk "without consideration of costs or other nonrisk factors." 15 U.S.C. § 2605(b)(4)(A). By excluding certain hazards, exposures, and conditions of use for reasons that bear no relationship to risk, EPA is considering nonrisk factors. For example, by excluding exposures because they could be regulated under another statute, EPA is considering a nonrisk factor.

Textually, EPA's approach also directly conflicts with TSCA § 26(k). 15 U.S.C. § 2625(k). TSCA § 26(k) requires EPA to "take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is reasonably available to the Administrator." *Id.* Congress included this provision to ensure that EPA could not ignore "reasonably available" "information relating to a chemical substance or mixture"; the purpose of this provision is to compel EPA to consider all reasonably available information. Congress also specified that EPA must consider the reasonably available "hazard and exposure information." It would undermine this directive if EPA chooses to ignore certain hazards or exposures.

ii) TSCA's overall structure requires EPA to consider all hazards, exposures, and conditions of use.

Moreover, EPA's pick-and-choose approach cannot be squared with the overall structure of TSCA.

As EPA reasoned in its proposed Risk Evaluation Rule, when discussing conditions of use, that TSCA "provides no criteria for EPA to apply" for selecting hazards, exposures, and conditions of use for analysis shows that the Agency does not have "license to choose" among those hazards, exposures, and conditions of use for analysis. 82 Fed. Reg. 7562, 7566 (Jan. 19, 2017). The precision with which Congress prescribed EPA's implementation of section 6 supports this reading. Section 6 lays out detailed directions for EPA. *See* 15 U.S.C. § 2605(b)(1)(A) (mandating considerations for priority designations), (b)(4)(D) (identifying risk factors to include in a risk evaluation's scope), (b)(4)(F)(i)-(v)

(detailing requirements for conducting risk evaluations); *see also id.* § 2605(a) (specifying possible risk management measures). These provisions indicate that Congress did not mean to allow EPA to exclude hazards, exposures, or conditions of use from risk evaluation without any criteria or instruction. *Cf. NRDC, Inc. v. EPA*, 863 F.2d 1420, 1432 (9th Cir. 1988) (invalidating regulatory procedure that "is wholly silent as to what factors the agency is to consider in granting exceptions" and provides "no discernible standard [for] limit[ing] th[at] discretion").

Indeed, when Congress intended EPA to exercise discretion under TSCA, it said so explicitly. *See, e.g.*, 15 U.S.C. §§ 2613(f) (granting EPA "[d]iscretion" in handling claims to protect confidential information), 2608(a) (instructing EPA, if it "determines, in the Administrator's discretion," that an unreasonable risk may be prevented under a federal law administered by another agency, to notify the agency), 2608(b), 2605(b)(4)(E)(iv)(II). That Congress purposefully included the language of discretion "in one section of the statute but omit[ted] it in another section of the same Act" shows that Congress did not intend EPA to use discretion to pick and choose which hazards, exposures, and conditions of use to consider in prioritization and risk evaluation. *Hernandez v. Ashcroft*, 345 F.3d 824, 834 (9th Cir. 2003) (quoting *Andreiu v. Ashcroft*, 253 F.3d 477, 480 (9th Cir. 2001) (en banc)).

Implicitly recognizing that Congress did not grant EPA boundless discretion to exclude exposures, EPA suggests that it will "focus its analytical efforts on exposures that are likely to present the greatest concern." *See, e.g.*, Problem Formulation for Perchloroethylene at 15. But no language in TSCA limits EPA to this "greatest concern" or "greatest potential for risk" focus. Nor does EPA point to any statutory terms that even arguably supply such a limitation.

TSCA's provisions direct EPA to prepare risk evaluations and the related findings for "chemical substances," as a whole, not for specific or limited hazards, exposures, or conditions of use of those substances. For example, the risk management provision expressly requires EPA to address risks when the risks arise from combined sources of exposure. TSCA § 6(a) provides that: "If [EPA] determines in accordance with [the risk evaluation provision] that the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, or that any combination of such activities, presents an unreasonable risk of injury to health or the environment," then EPA must issue a risk management rule. 15 U.S.C. § 2605(a); *see also* 15 U.S.C. § 2608(a) (using same language in provision governing requests to other federal agencies to address risks). Thus, if exposures resulting from "any combination" of conditions of use present an unreasonable risk, EPA must issue a risk management rule. But EPA must analyze *all* of the exposures resulting from these activities to assess whether *any combination* presents such a risk.

iii) TSCA's purpose, as well as basic logical reasoning and the best available science, require EPA to consider all hazards, exposures, and conditions of use to assess a chemical substance as a whole.

The purpose of the risk evaluation is to analyze the risks of a substance based on an assessment of its hazards and exposures. Ignoring potential exposures and hazards at the outset undermines that purpose. And science and logic do not support EPA's exclusions. As explained below in Sections 1.C and

5, EPA's exclusions of certain exposures result in incoherent problem formulations where EPA acknowledges ample evidence of exposure, for example, in the monitoring data, but then refuses to look at those very exposures in its final analysis. Willfully ignoring these exposures at the outset is contrary to the purpose of TSCA's risk evaluations, as well as the law's requirement that EPA rely on the best available science. EPA is imposing blinders on its analysis by asserting authority to refuse to look at certain exposures, including known exposures, and the result is that EPA is overlooking exposures in the real world. This approach is both contrary to law and arbitrary and capricious.

iv) The legislative history requires EPA to integrate a chemical's exposure and hazard information and nothing suggests that EPA can ignore existing exposures and hazards.

Numerous statements in the legislative history reveal that Congress intended for EPA to assess "risk" based on "the integration of hazard and exposure information about a chemical." S. Rep. No. 114-67 at 17 (June 18, 2015); 161 Cong. Rec. H4551 at H4556 (daily ed. June 23, 2015) ("The risk evaluation itself only asks does the chemical present an unreasonable risk of injury to health or the environment. That is a science question based on a combination of hazard and actual exposure."). Senator Vitter described an accurate assessment of risk as turning on integrating exposure and hazard information. *See* 162 Cong. Rec. S3511 at S3519 (daily ed. June 7, 2016) ("Exposure *potential*, when integrated with the hazard *potential* of a chemical, determines a chemical's potential for risk.") (emphases added). Congress intended for EPA to integrate all available information about exposure and hazard when assessing risk, as reflected in this history and the text of TSCA.

No statement in the legislative history suggests that EPA may ignore exposures or hazards when assessing the risk presented by a chemical substance. In its Risk Evaluation Rule, EPA relied on a floor statement from a single Senator to justify its interpretation that it had discretion to choose the conditions of use for analysis. 40 Fed. Reg. at 33,728 (citing 114 Cong. Rec. S3519-20 (daily ed. June 7, 2016) (statement of Sen. Vitter)). As EDF has previously explained,[3] the legislative history as a whole does not justify EPA's approach to conditions of use, but here EPA has even less basis for its approach; EPA has not pointed to any statement in the legislative history supporting its approach of ignoring certain exposures or hazards.

B. EPA's own risk evaluation rule requires that EPA consider all relevant hazards and all exposures under the conditions of use within the risk evaluation.

EDF disagrees with EPA's final Risk Evaluation Rule for numerous reasons, as discussed in our prior comments and in litigation challenging that rule. EDF reiterates and incorporates those points here. *See* Appendix A. Nonetheless, even EPA's final Risk Evaluation Rule requires EPA to consider all relevant hazards and exposures under the conditions of use within the risk evaluation. The Rule specifically requires that: "Relevant *potential* human and environmental hazards will be evaluated." 40 C.F.R. § 702.41(d)(3) (emphasis). Thus, EPA must consider any relevant "potential" hazards when preparing a risk evaluation. *See also* 40 C.F.R. § 702.41(d)(2) ("The hazard assessment process will identify the types

[3] EDF Comments on Ten Scopes under the Toxic Substances Control Act, pp.7-8, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069.

of hazards to health or the environment posed by the chemical substance under the condition(s) of use within the scope of the risk evaluation."). The Rule also requires that: "[e]xposure information related to potential human health or ecological hazards of the chemical substance will be reviewed in a manner consistent with the description of best available science and weight of scientific evidence." 40 C.F.R. § 702.41(e)(3). When preparing the risk characterization, EPA shall "[t]ake into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the condition(s) of use of the chemical substance." 40 C.F.R. § 702.43(a)(4). Thus, EPA must consider all hazards and all exposures under the conditions of use. None of these duties are qualified or provide an authority for EPA to exclude hazards or exposures from analysis.

Other provisions of the rule confirm this reading. EPA requires manufacturer requests for risk evaluations to "include or reference *all* available information on the health and environmental hazard(s) of the chemical substance, human and environmental exposure(s), and exposed population(s), as relevant to the circumstances identified in the request." 40 C.F.R. § 702.37(b)(4) (emphasis added). Thus, manufacturers must submit all available information on hazard and exposure under the identified conditions of use because EPA must consider all hazards and exposures when preparing risk evaluations.

In the preamble to the rule, EPA commits to considering all hazards and exposures under the conditions of use:

> The Administrator will consider relevant factors including, but not limited to: The effects of the chemical substance on health and human exposure to such substance under the conditions of use (including cancer and non-cancer risks); the effects of the chemical substance on the environment and environmental exposure under the conditions of use.

82 Fed. Reg. at 33,735. EPA thus committed to considering the "effects of the chemical substance on health and human exposure to such substance under the conditions of use." *Id.* These commitments are not qualified or accompanied by any assertion of discretion to ignore effects or exposure information under the conditions of use. EPA cannot fulfill this duty without considering all the hazards and sources of human exposure under the conditions of use.

Similarly, in the preamble, EPA states that "[u]sing reasonably available information, exposures will be estimated (usually quantitatively) for the identified conditions of use." 82 Fed. Reg. at 33,742. EPA cannot prepare an accurate quantitative estimate for exposure if EPA has excluded exposure pathways. "For environmental evaluations specifically, EPA plans to include a discussion of the nature and magnitude of the effects, the spatial and temporal patterns of the effects, [and] implications at the species, population, and community level." 82 Fed. Reg. at 33,743. EPA cannot accurately discuss the magnitude of the effects on the environment or the spatial and temporal patterns of those effects if EPA ignores the vast majority of the environmental exposures, as EPA proposes to do.

Moreover, in the preamble to the rule, while EPA went to great lengths to describe its alleged discretion to pick-and-choose conditions of use, EPA never stated that it had discretion to exclude hazards or exposures related to conditions of use within the risk evaluation. EPA's failure to assert any discretion

to exclude exposures and hazards reflects that EPA, in fact, lacks any such discretion. Similarly, in the preamble to the risk evaluation rule, EPA asserted that it had authority to ignore conditions of use under other agencies' jurisdiction. 82 Fed. Reg. at 33,729 (July 20, 2017). This is incorrect, but EPA never asserted that it had authority to ignore exposures under EPA's jurisdiction. Once again, EPA's silence on this issue in its rule highlights that EPA could not justify such discretion. In sum, EPA's arguments for excluding certain conditions of use cannot simply be extended mindlessly to exclude consideration of exposures and hazards. *See United States Sugar Corp. v. EPA*, 830 F.3d 579, 650 (D.C. Cir. 2016) (agency may not assume a rationale for one exemption identically applies elsewhere).

C. The problem formulations are incoherent and arbitrary and capricious because of EPA's approach to hazard, exposure, and conditions of use.

EPA's illegal approach to exposures leads it to put "blinders" on regarding risks. The result is "arbitrary, capricious, [or] an abuse of discretion" under the APA, 5 U.S.C. § 706(2)(A), because it will lead EPA to have considered "factors which Congress has not intended it to consider [and] entirely failed to consider an important aspect of the problem." State Farm, 463 U.S. at 43. It also violates several provisions of TSCA § 26 because by ignoring uses, exposures, hazards, and related information, EPA will not be acting "consistent with the best available science," EPA will not base decisions on "on the weight of the scientific evidence," and EPA will not "take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is reasonably available to the Administrator." 15 U.S.C. § 2625(h), (i), (k). In addition, because EPA's distinction is a false one untethered to the information, EPA seems to treat certain exposures inconsistently throughout the documents.

For example, as detailed more below, early in the problem formulations, EPA describes information revealing that these chemicals are released or disposed of through numerous environmental media and that exposures occur through numerous media. But EPA then systematically excludes many of these pathways of exposure from its future risk evaluation. Thus, EPA (correctly) describes the factual reality that exposures to humans and the environment occur through these environmental pathways. But EPA then imposes blinders on its analysis by excluding these pathways from further consideration. This is the definition of arbitrary and capricious conduct.

EPA's draft risk evaluations should indicate that it will assess the reasonably available information on hazards and exposures for the substances (see Section 8 below), and that information should inform EPA's evaluation of the risks of the chemicals. If there is a real-world or reasonably foreseen exposure or hazard, then EPA should not ignore it.

2. EPA should not refuse to further analyze exposure pathways on a cursory basis, and in any event, EPA still needs to consider those exposures when evaluating the combined exposures.

Throughout the problem formulations, EPA illegally decides not to analyze certain exposures further—effectively excluding certain exposure pathways—based on, at best, cursory, unpersuasive, and unsupported analyses (often contradicting other statements in the record). With these rushes to judgment, EPA all but concludes no unreasonable risk from certain exposures based on little analysis

and with no indication that it intends to revisit those exposures or risks in combination with those it does intend to analyze further.

As just one example, EPA plans to ignore the oral pathway of exposure to perchloroethylene for consumers based on an unsupported assertion that such exposure will be limited due to absorption and volatilization, *despite* the same problem formulation acknowledging that infants and children may well experience oral exposure through mouthing. *See* Problem Formulation for Perchloroethylene at pp. 57, 46. More examples of this problematic approach appear in the chemical-specific comments below.

When EPA declines to analyze a pathway further, EPA must have developed and applied a sound, rational basis for assessing the exposure level, supported by scientific evidence. In addition, EPA cannot then effectively ignore the exposure. Rather, EPA still must consider how the exposure may combine with other sources of exposure, so EPA must actually assess the level of exposure from the pathway individually and then consider how it combines with other sources of exposure.

3. EPA must analyze background exposures in all of the problem formulations.

In some but not all problem formulations, EPA indicates it will take into account background levels of exposure in various media. For example, in the HBCD problem formulation, EPA states:

> For HBCD, EPA plans to analyze background levels for indoor dust, indoor air, ambient air, surface water, sediment, soil, dietary food sources, aquatic biota, and terrestrial biota. EPA has not yet determined the background levels in these media or how they may be used in the risk evaluation.

Problem Formulation for HBCD at pp. 56-57. For HBCD, EPA similarly repeats its intention to look at background levels in its Exposure Conceptual Model. *Id.* at 99-105.

EPA needs to include consideration of such exposures in all of its problem formulations for the reasons articulated in Section 1. It is the total level of exposure to a chemical that determines risk, and this includes exposures that EPA is legally required to evaluate in its risk evaluations arising from conditions of use of a chemical, and exposures that, as EPA notes in the HBCD problem formulation, "are not generally attributable to any one use or source." *Id.* at 62.

However, EPA's consideration of background levels can in no way justify EPA's decisions to exclude various conditions of use and exposure pathways, which need to be included in the problem formulations and directly evaluated.

4. EPA should analyze past conditions of use because they are reasonably foreseen, while also developing significant new use rules for those conditions of use.

A. Past conditions of use are known to have occurred in the past and are certainly reasonably foreseen conditions of use, absent compelling evidence that they will not resume.

As argued further in Section 1, EPA must consider all conditions of use when preparing a risk evaluation under TSCA § 6, including so-called legacy uses, associated disposals, and legacy disposals. EDF has previously articulated these arguments and incorporates the arguments here.[4]

In several of the problem formulations, EPA has identified past conditions of use that it indicates it will exclude from its risk evaluations. Problem Formulation for Asbestos at pp. 19-21; Problem Formulation for 1,4-Dioxane at p. 18; Problem Formulation for HBCD at pp. 20-24. Past conditions of use that are not currently ongoing are "known" to have occurred in the past, and these conditions of use are definitely "reasonably foreseen." 15 U.S.C. § 2602(4). Congress included "reasonably foreseen" circumstances within TSCA with the express goal of ensuring that EPA swept more broadly than known (or intended) uses; EPA cannot evade that duty by limiting its analysis to conditions of use with evidence of current, ongoing use—such an interpretation would effectively limit EPA's analysis to "known" uses. While there may well be circumstances in which a use that is not currently occurring could be said to be not "reasonably foreseen" at this time, the term surely cannot be read in such a way that only uses that are known to be current are "reasonably foreseen" as that would read it out of existence and collapse the inquiry to one where a use must be "known" to be considered "reasonably foreseen."

Reasonably foreseen is a term of art with a long history in the law; it is well established under the law that "[a] natural and probable consequence is a foreseeable consequence. But to be reasonably foreseeable [t]he consequence need not have been a strong probability; a possible consequence which might reasonably have been contemplated is enough." *People v. Medina*, 209 P.3d 105, 110 (Cal. 2009) (internal citations and quotation marks omitted). Numerous courts have recognized that circumstances are reasonably foreseen when similar circumstances have occurred in the past. *See, e.g.*, *McKown v. Simon Prop. Grp., Inc.*, 344 P.3d 661, 663 (Wash. 2015); *Burns v. Penn Cent. Co.*, 519 F.2d 512, 515 (2d Cir. 1975). The fact that these conditions of use occurred in the past establishes that they are reasonably foreseen.

It is hard to see how the mere cessation of use, particularly if it ceased recently, is by itself sufficient to render the use not "reasonably foreseen." The concept of "reasonably foreseen" wraps in uses that have never before existed if there is a logical rationale for thinking that such a use could occur; if a use has actually occurred, but merely halted, it is clearly not speculation that the chemical substance being evaluated could be used in that way; it is only a question of how likely it is that the chemical could be used that way again. EPA, however, does not appear to have undertaken such analyses. Rather, in some problem formulations, the Agency seems to accept at face value assertions by industry in phone calls and other communications (that do not appear to be publicly available) that uses have ended, or

[4] EDF Comments on Ten Scopes under the Toxic Substances Control Act, pp. 4-11 (Sept. 2017), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069; *see also* Appendix A.

have ended and will not be resumed. Problem formulation for HBCD at pp. 20-24; Problem formulation for 1,4-Dioxane at p. 18. In some cases, EPA has not examined the reasons the use came to the end, while in others the reasons given are only assertions that merit closer scrutiny.

The time period in which a use is alleged to have ceased is sometimes only in the past few years, clearly within the statutory timeframe for a chemical substance to be deemed active under the Inventory Notification Rule required by § 8(b)(4)(A), where TSCA specifies a ten-year period dating from enactment back to June 22, 2006. 15 U.S.C. § 2607(b)(4)(A). While that time period is not directly applicable here, it would seem incongruous that a use that would lead to a chemical substance being deemed active, rather than inactive, could simply be disregarded without analysis when determining what circumstances of use are "reasonably foreseen."

As EPA itself acknowledged in its recently proposed significant new use rule for certain uses of asbestos, absent a regulation governing the resumption of an old condition of use, "the importing or processing of" a chemical for a past use that is no longer ongoing "may begin at any time." 83 Fed. Reg. at 26,927. Thus, the condition of use is reasonably foreseen absent a legal ban on it. Even if a chemical is no longer used for a particular condition of use, persons may resume past uses in response to economic, regulatory, or other changes. For example, in the problem formulation for 1-BP, EPA states that few dry cleaners still use 1-BP as a dry cleaning solvent, but EPA also acknowledges that it is reasonably foreseen that such use may increase in response to increasing regulation of perchloroethylene for that use. See Problem Formulation for 1-BP at p. 20. Similarly, other past conditions of use that have been phased out may resume in response to economic changes and regulatory shifts. *If* a chemical had a particular condition of use in the past, EPA should analyze that condition of use absent compelling evidence that the use will not resume in the future.

B. In the meantime, EPA should promulgate significant new use rules to govern past conditions of use as a stopgap measure.

For reasons articulated at length elsewhere in these comments (see Sections 1 and 4.A), EDF considers EPA's exclusions of past uses from its risk evaluations to be at odds with the requirements of TSCA, including because absent a regulatory ban they still constitute reasonably foreseen conditions of use of the chemicals. Such uses need to be included in the risk evaluations.

However, for uses that are no longer ongoing, EPA can and should – as a stopgap measure – promulgate significant new use rules (SNURs) requiring any company intending to commence manufacture or processing of a chemical for such a use to first notify EPA and requiring that EPA review the proposed activity to determine whether it may present an unreasonable risk.

EPA has proposed such a SNUR for uses of asbestos it has identified as no longer ongoing. 83 Fed. Reg. 26,922 (June 11, 2018). EDF provided comments on that SNUR, which we incorporate and reiterate here.[5] EDF recommends that EPA initiate the development of SNURs for uses of the other chemicals

[5] EDF Comments on Asbestos; Significant New Use Rule, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0159-1269.

addressed by the current problem formulations that are no longer ongoing, taking into account the important qualifications and recommendations included in our comments.

5. EPA cannot ignore ongoing, real-world exposures because they are occurring despite another EPA-administered statute that could potentially cover those exposures.

As established above, EPA must assess all hazards and exposures when evaluating the risk presented by a chemical substance. For this same reason, EPA must consider all real-world, intended, and reasonably foreseen exposures that occur even if they fall under the jurisdiction of other EPA-administered statutes. In all but one of the problem formulations, EPA states that "EPA does not expect to include in the risk evaluation pathways under programs of other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist." *See, e.g.*, Problem Formulation for NMP at p. 49.

Similar language appears in nine of the ten problem formulation documents. This approach is illegal and arbitrary and capricious for numerous reasons, including because TSCA requires EPA to analyze all exposures for the reasons discussed above. This approach also violates the text and structure of TSCA for additional reasons unique to this rationale for excluding exposures.

As discussed in more detail below, first and foremost this approach is factually and scientifically inaccurate. For numerous sources of exposure, EPA treats the overall exposure from a particular pathway as "zero" or non-existent despite the fact that the available evidence thoroughly establishes that exposure is occurring at levels well above zero regardless of any actions taken under the other statutes EPA invokes. Thus, in reality, human beings and the environment are experiencing levels of exposure that EPA is willfully ignoring. EPA is choosing to adopt false factual assumptions, and "[r]eliance on facts that an agency knows are false at the time it relies on them is the essence of arbitrary and capricious decisionmaking." *Animal Legal Def. Fund, Inc. v. Perdue*, 872 F.3d 602, 619 (D.C. Cir. 2017). This approach also violates the requirements to act "consistent with the best available science" and to "take into consideration information relating to a chemical substance or mixture, including hazard and exposure information, under the conditions of use, that is reasonably available to the Administrator." 15 U.S.C. § 2625(h), (k). Thus, for example, in its problem formulation for perchloroethylene, EPA states that its inclusion criteria for data sources reporting environmental fate data expressly do not include consideration of "fate endpoints, associated processes, media and exposure pathways" "to human and ecological receptors from environmental releases and waste stream [sic] associated with industrial and commercial activities," in violation of the duty to consider all reasonably available information. *See* Problem Formulation for Perchloroethylene at p. 160. The problem formulations do not establish that the regulation of these chemical substances under other statutes will eliminate exposures, and in fact, the problem formulations and publicly available evidence all establish that exposures continue to occur in the real-world despite these statutes. EPA cannot ignore those exposures.

In addition, EPA must consider the possibility that these exposures, *combined with other sources of exposure*, could present an unreasonable risk. EPA's decision to ignore exposures one-by-one rather

than look at combined exposure is inherently inaccurate and will invariably lead to an underestimation of exposure and risk.

Furthermore, EPA has not established that these environmental statutes "adequately assess and effectively manage exposures." EPA's bald assertions to the contrary do not make it so. In any event, that is not the legally correct standard under TSCA. As explained below, EPA can only rely on statutory authorities other than TSCA in compliance with TSCA § 9 (notably, the TSCA § 9 process occurs after EPA has completed a comprehensive risk evaluation finding unreasonable risk). To comply with TSCA § 9, EPA must find that those authorities eliminate the risks EPA has previously identified or reduce them to a sufficient extent under TSCA § 9(b)(1), and TSCA requires that EPA reduce risk "to the extent necessary so that [the chemical] no longer presents [an unreasonable risk of injury to health or the environment]." *See* 15 U.S.C. §§ 2608(b)(1), 2605(a). In addition, under TSCA § 9(b)(2) EPA must consider "all relevant aspects of the risk" when deciding whether to regulate under TSCA or another statute. *Id*. § 2608(b)(2). EPA has not met any of these standards in the problem formulations, and EPA's statements that the exposures are adequately assessed and effectively managed under other statutes are legally irrelevant (even if they were true).

When relying on these other statutory authorities, EPA merely provides a list of various regulatory standards and criteria that EPA indicates apply or could apply to certain sources of the chemicals. EPA provides no analysis whatsoever as to: the extent to which the standards or criteria cover the full range of exposure to the chemical through the pathway; the extent and magnitude of releases of the chemical allowed under each of the regulatory standards or criteria; or any other factors that would be necessary to analyze to determine the extent and nature of potential risk allowed under the standards. In particular, TSCA § 6(b)(4)(F)(iv) requires that, in conducting a risk evaluation, EPA evaluate "the likely duration, intensity, frequency, and number of exposures," 15 U.S.C. § 2605(b)(4)(F)(iv), including exposures resulting from those allowable emissions, discharges, or releases. EPA needs to provide this analysis, and EPA cannot simply point to regulation under another statute to bypass the analysis. EPA has also not acknowledged, let alone analyzed, the overall risks to the general population or to vulnerable subpopulations due to the combination of exposures arising from the various sources for which standards exist, not to mention in combination with additional emission sources not subject to any standard. EPA has made no attempt to reconcile any such risk with that allowed under TSCA.

EPA offers only vague claims, such as that EPA "as appropriate, has reviewed, or is in the process of reviewing remaining risks." No specifics as to the status of or timeline for such reviews have been provided, and no indication is made as to when and on what basis such reviews are deemed "appropriate." Nor have the results of any such reviews, if they have been completed, been provided, let alone analyzed in the context of TSCA's requirements.

At a minimum, EPA has completely failed to establish that these statutes reduce exposure to zero. To the contrary, it is thoroughly clear that humans and the environment continue to experience significant exposures through the excluded pathways. To prepare a scientifically accurate risk evaluation, EPA must analyze the exposures through those pathways.

A. The text and overall structure of TSCA makes it clear that EPA has to analyze exposures, even if they have been or could be assessed under another statute.

In contrast to the scoping documents, EPA now asserts that it has discretion to exclude "certain exposure pathways that fall under the jurisdiction of other EPA-administered statutes." *See, e.g.*, Problem Formulation for Perchloroethylene at p. 15. But EPA provides no textual basis for ignoring those exposures. Instead, in a footnote, EPA cites to its discussion regarding "conditions of use," but even assuming for the sake of argument that EPA has authority to exclude conditions of use, such power does not justify excluding exposures related to conditions of use still within the scope of the risk evaluation, as EPA proposes to do. Nothing in TSCA's risk evaluation provision authorizes EPA ignoring exposures because of other statutory authorities, and as explained above, EPA has to analyze all exposures including these exposures. And several other provisions of TSCA indicate that Congress intended for EPA to consider such exposures, except to the extent Congress explicitly provided otherwise.

First, Congress expressly excluded certain chemicals or uses of chemicals regulated under other statutes when it defined "chemical substance" in TSCA § 3(2). 15 U.S.C. § 2602(2)(B). For example, "chemical substance" does not include "any pesticide (as defined in the Federal Insecticide, Fungicide, and Rodenticide Act) when manufactured, processed, or distributed in commerce for use as a pesticide." *See id*. § 2602(2)(B)(ii). Thus, when Congress intended for EPA not to regulate certain exposures because they were regulated under other specific EPA-administered statutes, Congress expressly excluded those exposures. That Congress chose a limited, specific set of exclusions indicates that Congress did not intend for EPA generally to ignore other exposures where they fall under other federal regulatory schemes.

Second, in TSCA's risk evaluation provision, Congress specifically intended for EPA to "conduct risk evaluations *** to determine whether a chemical substance presents an unreasonable risk of injury to *** the environment," 15 U.S.C. § 2605(b)(4)(A), but EPA's approach has eliminated almost all analysis of environmental exposures. EPA has largely read the requirement to evaluate risks to the environment out of the statute, but this approach violates a fundamental tenant of statutory interpretation. A. SCALIA & B. GARNER, READING LAW: THE INTERPRETATION OF LEGAL TEXTS 174 (2012) ("If possible, every word and every provision is to be given effect *** None should needlessly be given an interpretation that causes it to duplicate another provision or to have no consequence."). Moreover, Congress enacted this requirement that EPA analyze risks to the environment against the backdrop of the existing environmental statutes; if Congress had considered them per se sufficient, Congress would not have included this mandate in TSCA. But Congress did.

Third, Congress specifically directed EPA to analyze the risks of chemicals presented "under the conditions of use," and Congress consciously decided to specify that "disposal" is a condition of use under TSCA. "Conditions of use" expressly includes "the circumstances *** under which a chemical substance is intended, known, or reasonably foreseen to be to be manufactured, processed, distributed in commerce, used, or *disposed of*." 15 U.S.C. § 2602(4) (emphasis added). In the problem formulations, EPA systematically excludes exposures through disposal based on a variety of theories,

and in doing so, EPA is ignoring Congress's direction that it assess risks associated with the conditions of use, including disposal. Similarly, EPA is ignoring exposures from other conditions of use, such as "manufactur[ing]," "process[ing]," and potentially distribution in commerce, by for example ignoring the emissions from the manufacturing and processing facilities. Congress expressly included all of these circumstances within the definition of "conditions of use," and EPA should not ignore the exposures resulting from them.

Fourth, TSCA § 9(b) provides that EPA "shall coordinate *actions* taken under [TSCA] with *actions* taken under other Federal laws administered in whole or in part by the Administrator." 15 U.S.C. § 2608(b) (emphases added). While EPA is supposed to coordinate the "actions" under each statute, this provision does not contemplate EPA excluding exposures from the analyses prepared under TSCA. Indeed, the remaining language of TSCA § 9(b) highlights that Congress intended for EPA to prepare risk evaluations analyzing all exposures, including those that might be addressed under another authority.

Under TSCA § 9(b)(1), EPA can only choose to rely on other authorities "[i]f [EPA] determines that a risk to health or the environment associated with a chemical substance or mixture *could be eliminated or reduced to a sufficient extent* by actions taken under the authorities contained in such other Federal laws." 15 U.S.C. § 2608(b)(1) (emphasis added). Thus, Congress provided a standard that EPA must meet before relying on other authorities: with respect to the "risk to health or the environment" presented by a chemical, the other authority must either "eliminate[]" that risk or "reduce [the risk] to a sufficient extent." *Id.* Reduction in risk must be "sufficient" as defined by TSCA, and the word "extent" cross-references the basic standard set forth in section 6(a). *See* 15 U.S.C. § 2605(a). Section 6(a) provides that if EPA determines that a substance or mixture "presents an unreasonable risk of injury to health or the environment," EPA "shall" apply requirements to the "substance or mixture to the extent necessary so that the chemical substance or mixture no longer presents such risk." *Id.* Thus, EPA may only rely on actions under another statute if those actions will reduce an identified risk "to the extent necessary so that [it] no longer presents [an unreasonable risk of injury to health or the environment]." EPA cannot assume that other statutes, with different standards, meet the requirements of TSCA.

TSCA requires that EPA eliminate the "unreasonable risk," *id.* and that unreasonable risk of injury to health or the environment must be identified under TSCA § 6(b)(4)(A) "without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation identified as relevant to the risk evaluation by the Administrator." 15 U.S.C. § 2605(b)(4)(A). Thus, TSCA's standard requires EPA to resolve risks identified without consideration of costs or other nonrisk factors, and EPA must specifically consider risks to vulnerable subpopulations. Generally speaking, the other EPA-administered statutes do not have this same standard. Some of these statutes allow consideration of nonrisk factors and do not explicitly require consideration of vulnerable subpopulations. EPA cannot simply assume that regulatory efforts that meet the requirements of those statutes will also meet TSCA's requirement that EPA eliminate unreasonable risks. And Congress's decision to enact the TSCA standard reflects that Congress wanted EPA, when implementing TSCA, to meet that standard; EPA cannot rely on its fulfillment of a different standard under a different statute to evade that duty.

Under TSCA § 9(b)(2) Congress directed EPA to consider certain factors to resolve overlaps in EPA's statutory jurisdictions after completing the risk evaluation. Specifically, in determining whether to address a risk under TSCA or another statutory authority administered by EPA, EPA "shall consider, based on information reasonably available to the Administrator, all relevant aspects of the risk," among other things. *Id.* § 2608(b)(2). Thus, EPA has to analyze "all relevant aspects of the risk" in its risk evaluations, *before* deciding whether to address particular risks through TSCA or another statutory authority. Congress would not have included this requirement if Congress had meant for EPA to simply defer to current regulatory approaches to those chemicals at the outset before conducting a risk evaluation.

Among other concerns, if EPA just ignores risks arising from exposures that fall within other statutes' jurisdiction, then EPA will lack the information necessary to prepare the necessary analyses under TSCA § 9(b)(2). TSCA § 9(b) clearly contemplates that EPA will analyze all these exposures in risk evaluations and then meet its duties under TSCA § 9(b) based, in part, on the analyses prepared in the risk evaluations. As reflected in TSCA § 6, Congress expressly chose to separate risk evaluation and risk management into different procedural steps (with risk evaluation preceding risk management), to ensure that EPA provided a robust risk evaluation uncolored by nonrisk factors or other risk management concerns.

Notably, in its problem formulations, EPA makes no showing that its actions under other statutes reduce the risk "to the extent necessary so that [it] no longer presents [an unreasonable risk of injury to health or the environment]," and EPA does not present any actual analysis of "all relevant aspects of the risk" arising from the ignored exposures. So EPA has undisputedly failed to comply with TSCA § 9(b). Given that Congress expressly addressed the issue of overlapping regulatory jurisdictions in TSCA § 9, EPA cannot avoid those procedures by simply ignoring exposures that fall within another statute's jurisdiction.

Furthermore, EPA is expressly required to evaluate exposures from combinations of activities, which it cannot do if it excludes some exposures at the outset that may be able to be addressed under another authority, particularly when any risk management under the other authority would not reduce exposure to zero.

B. EPA's approach to the general population and subpopulations highlights that its decision to exclude exposures under other EPA-administered statutes is illegal and arbitrary and capricious.

i) EPA must analyze whether 1,4-dioxane, carbon tetrachloride, methylene chloride, N-methylpyrrolidone, perchloroethylene, and trichloroethylene present a risk to the general population because the record establishes that the general population is exposed to these chemicals.

EPA states that it will not analyze general population exposures for 1,4-dioxane, carbon tetrachloride, methylene chloride, N-methylpyrrolidone (NMP), perchloroethylene, and trichloroethylene (TCE) because EPA considers its existing regulatory programs sufficient. Problem Formulation for 1,4-Dioxane

at p. 49; Problem Formulation for Carbon Tetrachloride at p. 56; Problem Formulation for DCM at p. 65; Problem Formulation for NMP at p. 59; Problem Formulation for Perchloroethylene at p. 73; Problem Formulation for TCE at p. 62.

EPA's approach is illegal for the reasons given above. In addition, the reasonably available information establishes that the general population experiences significant exposures to these chemicals, and it is irrational to ignore those exposures in light of this evidence. For example:

For 1,4-dioxane: EPA acknowledges that the general population may be exposed from inhalation of ambient air, through drinking water, and exposure during washing and bathing. Problem Formulation for 1,4-Dioxane at p. 31.

For carbon tetrachloride: EPA's first-tier analysis suggests that 6% of reported facility discharge levels result in drinking water estimates above EPA's minimum contaminant level. *See* Problem Formulation for Carbon Tetrachloride at p. 38.

For NMP: "Oral exposure to NMP is expected to be a relevant route of exposure for the general population. Individuals may be exposed to NMP levels that occur in drinking water and/or well water." Problem Formulation for NMP at p. 36.

For methylene chloride: "Due to its variety of uses and subsequent release to the environment, methylene chloride is present and measurable through monitoring in a variety of environmental media including ambient and indoor air, surface water and ground water, including sources used for drinking water supplies, sediment, soil and food products." Problem Formulation for DCM at p. 35. "[L]evels of methylene chloride in the ambient air are widespread and shown to be increasing." *Id*. at 39.

For perchloroethylene: "A subset of National Health and Nutrition Examination Survey (NHANES) data (1999-2000) reported in Lin et al. (2008) show the presence of perchloroethylene in 77% of human blood samples from non-smoking U.S. adults." Problem Formulation for Perchloroethylene at p. 42. Perchloroethylene also is a common contaminant in air, soil, surface water, and drinking water, and EPA cannot ignore those exposures which are occurring under its existing regulatory regimes.

For trichloroethylene: "TCE is one of the most frequently detected organic solvents in U.S. ground water. The U.S. Geological Survey (USGS) conducted a national assessment of VOCs in ground water, including TCE. Between 1985 and 2001, the detection frequency of TCE was 2.6%, with a median concentration of 0.15 µg/m3 (U.S. EPA, 2011c; Zogorski et al., 2006)." Problem Formulation for TCE at p. 34. "TCE has been detected in drinking water systems through national and state-wide monitoring efforts." *Id*. at 34. "The Third National Health and Nutrition Examination Survey (NHANES III) analyzed blood concentrations of TCE in non-occupationally exposed individuals in the United States and found that 10% of those sampled had TCE levels in whole blood at or above the detection limit of 0.01 ppb (U.S. EPA, 2011c)." *Id*. "The general population may ingest TCE via contaminated drinking water and other ingested media. It is anticipated that ingestion of drinking water containing TCE, for on-going TSCA uses, represents the primary route of oral exposure for this chemical." *Id*. at 38.

Given ample evidence that the general population in fact experiences exposures to these chemicals under EPA's current regulatory regimes, it is arbitrary and capricious for EPA to adopt an approach to risk evaluation that disregards the risks presented to the general population.

ii) EPA cannot accurately evaluate potentially exposed or susceptible subpopulations such as fenceline communities if EPA excludes the vast majority of exposure pathways leading to their greater exposure.

In numerous problem formulations, EPA correctly recognizes that a potentially exposed or susceptible subpopulation includes those "groups of individuals within the general population who may experience greater exposures due to their proximity to conditions of use identified in Section 2.2 that result in releases to the environment and subsequent exposures (e.g., individuals who live or work near manufacturing, processing, distribution or use sites)." *See, e.g.*, Problem for Perchloroethylene at p. 47. But EPA then plans to ignore the vast majority of pathways that cause these groups to face greater exposures—such as through releases to air, water, and land. EPA provides no rational explanation for how it will accurately and effectively evaluate the actual risk faced by these subpopulations while ignoring these exposures. Moreover, EPA's (correct) recognition that these groups face greater exposure highlights that it is irrational for EPA to ignore the pathways leading to these exposures.

In addition, as EPA correctly recognizes, TSCA specifically requires that EPA protect these subpopulations because they face greater exposure. And, EPA's existing regulations under other statutes, which may not have been developed with a focus on these particular subpopulations, may not always be "sufficient" under the TSCA standard.

C. The listing of asbestos, 1-4 dioxane, carbon tetrachloride, methylene chloride, perchloroethylene, and trichloroethylene as hazardous air pollutants does not result in zero exposures to them through the air pathway; EPA should analyze the real-world exposures.

EPA excluded exposures to asbestos, 1-4 dioxane, carbon tetrachloride, methylene chloride, perchloroethylene, and trichloroethylene through the air pathway because they are listed as hazardous air pollutants (HAP) under the Clean Air Act (CAA). Problem Formulation for Asbestos at p. 42; Problem Formulation for 1,4-Dioxane at pp. 42-43; Problem Formulation for Carbon Tetrachloride at p. 48; Problem Formulation for DCM at p. 54; Problem Formulation for Perchloroethylene at pp. 59-60; Problem Formulation for TCE at p. 54.

This approach is unreasonable for the reasons given above, but in addition, EPA has not made the necessary showing that the established HAPs eliminate any unreasonable risk and EPA has not assessed all relevant aspects of the risk. As EPA acknowledges in each of these problem formulations, the listing as a HAP leads to a technology-based standard for certain stationary sources. *See, e.g.*, Problem Formulation for Asbestos at p. 42. Such regulations do not necessarily eliminate exposures. Moreover, EPA is relying on "technology-based" standards, but under TSCA § 9, EPA can only rely on another statutory authority if it reduces exposures "to a sufficient extent" under TSCA, 15 U.S.C. § 2608(b)(1), and TSCA specifically requires that EPA eliminate the unreasonable risk, see 15 U.S.C. § 2605(a), without

reference to technology. EPA cannot assume that other statutes, with different standards, meet the requirements of TSCA.

i) EPA's Clean Air Act authority is not a comprehensive substitute for TSCA.

EPA's mandate to control toxic air pollutants under the Clean Air Act (CAA) differs from TSCA's provisions applicable to the same substances and thus does not presumptively address the same scope of risks. EPA points to CAA Sections 111 and 112, 42 U.S.C. §§ 7411-12, as an adequate proxy for TSCA regulations that would address the "ambient air pathway" of exposure to toxic air pollutants covered under both statutes, yet the statutory structures that empower EPA to control these pollutants through CAA regulation are different from EPA's authority to regulate or even prohibit the production or use of these substances under TSCA.

CAA Sections 111 and 112 differ in scope and approach as compared to TSCA. EPA points to CAA Section 112 which requires EPA to promulgate regulations applicable to sources of listed hazardous air pollutants including: 1,4-dioxane, carbon tetrachloride, methylene chloride, trichloroethylene, and perchloroethylene. Section 112 instructs EPA to list and regulate substances for which "emissions, ambient concentrations, bioaccumulation or deposition of the substance are known to cause or may reasonably be anticipated to cause adverse effects to human health or adverse environmental effects." 42 U.S.C. § 7412(b)(2). As EPA acknowledges, under the CAA "For stationary source categories emitting [Hazardous Air Pollutants] HAP, the CAA requires issuance of technology-based standards and, if necessary, additions or revisions to address developments in practices, processes, and control technologies, and to ensure the standards adequately protect public health and the environment." Problem Formulation for Perchloroethylene at p. 59. Under section 112(d)(1), EPA sets source-specific "standards for each category or subcategory of major sources and area sources of hazardous air pollutants listed." 42 U.S.C. § 7412(d)(1). This source-specific regulatory scheme requires EPA to:

> require the maximum degree of reduction in emissions of the hazardous air pollutants subject to this section (including a prohibition on such emissions, where achievable) that the Administrator, taking into consideration the cost of achieving such emission reduction, and any non-air quality health and environmental impacts and energy requirements, determines is achievable for new or existing sources in the category or subcategory to which such emission standard applies.

Id. § 7412(d)(2). This approach reflected in section 112 is distinct from TSCA which empowers EPA look at the risk posed by the chemical broadly without necessarily focusing on source-specific technology, costs of regulation, or what standards are "achievable" for each source category. Indeed, as explained previously, TSCA requires that EPA evaluate a chemical's risk "without consideration of costs or other nonrisk factors." 15 U.S.C. § 2605(b)(4)(A). In addition, TSCA requires EPA to consider the "conditions of use" of a chemical, with no distinction drawn between stationary sources and other sources. As a result, EPA cannot presumptively assume that section 112 regulation would necessarily address all the risks that TSCA requires the agency to identify and ameliorate.

Similarly, EPA points to CAA Section 111, 42 U.S.C. § 7411, as a basis for declining to evaluate risks associated with the ambient air pathway under TSCA. But, like section 112, section 111 differs in material respects from the approach embodied in TSCA. Section 111 requires EPA to set and periodically update standards of performance for categories of new stationary sources and existing stationary sources of pollution that cause or contribute "significantly, to air pollution which may reasonably be anticipated to endanger public health or welfare." 42 U.S.C. § 7411(b). In setting "standard[s] of performance" for each source category or even sub-category of sources, EPA must select a standard that "reflects the degree of emission limitation achievable through the application of the best system of emission reduction which (taking into account the cost of achieving such reduction and any nonair quality health and environmental impact and energy requirements) the Administrator determines has been adequately demonstrated." 42 U.S.C. § 7411(a)(1). TSCA's regime likewise diverges from this approach in its focus on the risks posed by chemical substances and EPA actions that can ameliorate those risks.

In addition to these substantive differences, existing standards under sections 111 and 112 are subject to different procedural requirements. For example, the CAA's source-specific standards under Section 111 are structured around a series of 8-year intervals for review and Section 112's list of substances is reviewed every 5 years, along with other periodic reviews called for under Section 112. EPA is also subject to a series of consent decrees for required reviews under Section 112(f)(2) and Section 112(d)(6), often setting longer timelines for new rulemaking. As a result, many of the category specific regulations under these provisions are in various stages of being updated. Accordingly, even if there were some substantive alignment between TSCA and the CAA provisions EPA cites—which is not the case, as we describe above—it would be manifestly arbitrary and capricious for the Agency to determine that CAA standards that have not been updated for many years, or even decades, presumptively discharge EPA's present-day responsibility to assess the risks these chemicals pose under TSCA.

ii) The problem formulations contain information establishing that there is exposure through ambient air.

Indeed, the problem formulations themselves establish that exposures through air persist for these chemicals despite any regulation under the CAA, and it is arbitrary and capricious for EPA to ignore those exposures. For EPA to treat these exposure levels as "zero" when they are known not to be does not comport with the best available science. For example:

For asbestos: EPA acknowledges that asbestos fibers occur in the air, with a 10-fold higher concentration of asbestos in cities (0.0001 fibers/ml) than in rural areas (0.00001 fibers/ml). Problem Formulation for Asbestos at p. 29.

For 1,4-dioxane: EPA states that a total of 62,596 lbs of the chemical were released to the air in 2015 according to the EPA Toxics Release Inventory (TRI). Problem Formulation for 1,4-Dioxane at p. 26. Both indoor and outdoor monitoring detected 1,4-dioxane. *Id*. at 28. "Of a total of 1397 collected samples, there were 948 non-detects (68%) and 449 detections (32%), which ranged from 0.005 to 0.96 ppb." Id.

For carbon tetrachloride: EPA states that a total of 104,838 lbs of the chemical were released to the air in 2015 according to TRI. Problem Formulation for Carbon Tetrachloride at p. 33. "According to the 2015 National Air Toxics Inventory, ambient air monitoring trends from 2003 to 2013 have shown that *** carbon tetrachloride average concentrations have slightly increased in the atmosphere over the 10-year period." *Id*. at 34.

For methylene chloride: EPA states that a total of 2,542,146 lbs of the chemical were released to the air in 2015 according to TRI. Problem Formulation for DCM at p. 34. "Ambient air samples worldwide have shown measured levels of methylene chloride." *Id*. at 35. EPA reports "monthly mean concentrations ranging from approximately 30-80 parts per trillion" in the mid-latitude northern hemisphere, with concentrations remaining the same or increasing with time. *Id*.

For perchloroethylene: EPA states that a total of 714,631 lbs of the chemical were released to the air in 2015 according to TRI. Problem Formulation for Perchloroethylene at p. 38. "EPA air monitoring data from 2013 reported detection of perchloroethylene in 77% of ambient air samples, with 58% of detects above the method detection limit. Indoor air concentrations of perchloroethylene tend to be greater than concentrations in outdoor air." *Id*. at 40. "[P]erchloroethylene was measured in 44.3% of 555 homes in three US cities. In this study, the median concentration was 0.56 µg/m3 and the 99th percentile was 20.9 µg/m3." *Id*. at 41.

For trichloroethylene: EPA states that a total of 1,880,569 lbs of the chemical were released to the air in 2015 according to TRI. Problem Formulation for TCE at p. 32. "TCE has been detected in ambient air across the United States, though ambient levels vary by location and proximity to industrial activities. *** A summary of the ambient air monitoring data for TCE (i.e., measured data) in the United States from 1999 to 2006 suggests that TCE levels in ambient air have remained fairly constant in ambient air for the United States since 1999, with an approximate mean value of 0.23 µg/m3." *Id*. at 33. EPA also mentions a number of studies reporting indoor air levels of TCE in residences, schools, and stores. *Id*. at 34.

iii) Additional information sources reveal that exposures through ambient air are occurring, and these additional information sources indicate that EPA's current analyses underestimate the exposure level through this pathway.

Moreover, EPA should not limit its analysis of air emissions to TRI data. EPA should also consider the data available from the National Emissions Inventory (NEI), which tend to reveal significantly greater levels of air emissions of, and thus air pathway exposures to, these chemicals. EPA cannot reasonably ignore this available information about air emissions and resulting exposures of these chemicals. As revealed in the below chart, despite the Clean Air Act protections, there are significant annual emissions and thus exposures through the air pathway for these chemicals.

	TRI 2016			NEI 2014
Chemical	**Fugitive Air Emissions (lbs)**	**Point Source Air Emissions (lbs)**	**TOTAL**	**(lbs)**
1,4-Dioxane	10,522	45,210	55,732	134,484
Asbestos (Friable)	106	178	284	1,561
Carbon tetrachloride	38,719	332,945	371,664	203,889
Dichloromethane (DCM)	1,272,089	1,335,196	2,607,285	14,271,645
Tetrachloroethylene (Perc)	313,197	354,705	667,902	7,941,891
Trichloroethylene (TCE)	1,442,918	687,349	2,130,267	12,191,695

EPA should analyze these exposures and the risks they present to both human health and the environment, including terrestrial species. With more than 14 million lbs of methylene chloride and more than 12 million lbs of trichloroethylene emitted to the air in 2014, it is absurd to treat the overall exposure through this pathway as if it were "zero."

Moreover, EPA should be collecting and analyzing information about exposure levels through the ambient air pathway, particularly near sites where people may experience greater exposure due to their proximity to conditions of use or contamination sites. As just one example, recently, a professional environmental engineering company measured exposures to perchloroethylene and trichloroethylene in Franklin, Indiana, in the ambient air, finding perchloroethylene at 171.73 µg/m3 and trichloroethylene at 52.61 µg/m3.[6] The firm also measured these chemicals in 14 different residences, finding additional indoor air exposures. By excluding pathways such as the ambient air pathway, EPA will seriously underestimate the levels of exposure.

In addition, this particular example highlights that EPA cannot adequately assess the risks faced by subpopulations consisting of people experiencing greater exposure due to their proximity to conditions of use without assessing pathways such as the ambient air pathway. If EPA ignores the ambient air pathway, EPA will completely ignore these exposure levels in Franklin, Indiana, and potentially similar exposure levels at locations across the country. EPA should use its information authorities to obtain

[6] *See* Edison Wetland Association, 2018 Residential Vapor Sampling "Mundell" Report p.9, https://www.edisonwetlands.org/johnson-county-in.

additional information about exposure levels experienced by the subpopulations living near conditions of use.

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Given evidence of real-world exposure through the air pathway, EPA must evaluate those exposures in its risk evaluations. In particular, EPA needs to consider whether these exposures combine with other sources of exposure in a manner that leads to an unreasonable risk, including to certain subpopulations. EPA cannot rationally exclude these exposures from its analysis.

D. Real-world exposures still occur through drinking water, and EPA cannot ignore those real-world exposures when assessing the risk presented by a chemical substance.

Based on various rationales, EPA decided to effectively ignore all exposures through drinking water for all ten chemicals. The systematic decision to ignore all exposures through this pathway is arbitrary and capricious because the available evidence reveals that exposures do occur through this pathway. Analyzing exposure through drinking water is also particularly important for EPA to obtain an accurate estimate of the exposure of infants and children, often a potentially exposed or susceptible subpopulation. *See, e.g.*, Problem Formulation for Perchloroethylene at p. 48 ("Drinking water could be a significant source of perchloroethylene ingestion exposure for children, who drink roughly four times as much water as adults.").

i) The existence of a Maximum Contaminant Level does not result in zero exposures to asbestos, carbon tetrachloride, methylene chloride, perchloroethylene, and trichloroethylene through drinking water; EPA should analyze the real-world exposures.

EPA will exclude exposures to asbestos, carbon tetrachloride, methylene chloride, perchloroethylene, trichloroethylene through drinking water because EPA has set an enforceable Maximum Contaminant Level (MCL) under the Safe Drinking Water Act (SDWA). Problem Formulation for Asbestos at pp. 42-43; Problem Formulation for Carbon Tetrachloride at pp. 48-49; Problem Formulation for DCM at p. 54; Problem Formulation for Perchloroethylene at p. 60; Problem Formulation for TCE at p. 54.

This approach is unreasonable for the reasons given above, but in addition, EPA has not made the necessary showing that the established MCLs eliminate any unreasonable risk and EPA has not assessed all relevant aspects of the risk. As EPA itself acknowledges in each of these problem formulations, the MCLs are only set at the level "feasible" which "refers to both the ability to treat water to meet the MCL and the ability to monitor water quality at the MCL." *See, e.g.*, Problem Formulation for Asbestos at p. 43. Thus, MCLs are based on non-risk factors and do not necessarily eliminate exposures.

Specifically, the contaminant level set under the SDWA considers "non-risk" factors, and the MCL is not sufficient to eliminate risks. While EPA must set a maximum contaminant level goal (MCLG) that is fully protective of health for drinking water contaminants, 42 U.S.C. § 300g-1(b)(1)(E); *see also* 42 U.S.C. § 300g-1(b)(4)(A), the MCLG is not the national drinking water standard. Rather, the agency must establish a maximum contaminant level (MCL) that is as close to the MCLG "as is feasible," considering

technological limitations and costs, and promulgate a national primary drinking water regulation (NPDWR) for the contaminant based on the MCL. 42 U.S.C. § 300g-1(b)(4)(B). In other words, the contaminant level EPA actually sets for safe drinking water is less protective than the MCLG because it accounts for feasibility and costs, which are non-risk factors that EPA may not consider during the risk evaluation process.

Chemical	**MCLG (mg/L)**	**MCL (mg/L)**
Asbestos	7 million fibers per liter (MFL)	7 MFL
Carbon tetrachloride	0	.005
Methylene Chloride	0	.005
Perchloroethylene	0	.005
Trichloroethylene	0	.005

Notably, the MCLG for four of these chemicals is zero, indicating that in order to avoid adverse effects on human health from drinking water EPA believes that these contaminants should not be in drinking water at any level. Because the MCL for these chemicals is higher, EPA must, among other things, address in the draft risk evaluation the risks posed by ongoing exposure to the chemicals at levels in drinking water below the MCL.

EPA has also failed to amend the MCLs for two of these chemicals, even though EPA has identified them as appropriate for revision. EPA is required to review and revise the drinking water standards every six years, as appropriate. 42 U.S.C. § 300g-1(b)(9). EPA's second six-year review of the NPDWRs concluded that the NPDWRs for trichloroethylene and perchloroethylene are candidates for regulatory revision.[7] More specifically, for both chemicals EPA stated that based on occurrence/exposure data and their cancer classifications "a revision to the MCL may provide a meaningful opportunity to reduce public health risks."[8] EPA also indicated that "analytical feasibility could be as much as 10 times lower (~ 0.0005 mg/L)" for both chemicals.[9] At this level, occurrence of both chemicals is "relatively widespread."[10]

However, it does not appear that EPA has done anything to act on this decision. Rather, EPA's website indicates that "a health assessment is in process [and] new analytical feasibility and treatment

[7] 75 Fed. Reg. 15,500 (Mar. 29, 2010), https://www.federalregister.gov/documents/2010/03/29/2010-6624/national-primary-drinking-water-regulations-announcement-of-the-results-of-epas-review-of-existing.
[8] *Id.* at 15,565 (TCE), 15,558 (perchloroethylene).
[9] *Id.* at 15,565 (TCE), 15,558 (perchloroethylene).
[10] *Id.* at 15,565 (TCE), 15,558 (perchloroethylene).

technology information may justify a revision."[11] It has now been eight years since EPA first identified these chemicals for revision, and nothing has been done. Since that time, EPA has conducted its third six-year review of the NPDWRS and specifically excluded TCE and perchloroethylene from that review because they were subject to "recently completed, ongoing or pending regulatory actions."[12] 82 Fed. Reg. 3518, 3520 (Jan. 11, 2017). Yet there is no indication that EPA is taking any action on these two chemicals.

In addition, the SDWA does not regulate all sources of drinking water. It is estimated that more than 13 million households rely on private wells for drinking water in the United States.[13,14] The national drinking water standards established under the SDWA do not apply to private wells. *See* 42 U.S.C. § 300f(1) (a "primary drinking water regulation" only applies to "public water systems"); 42 U.S.C. § 300f(4)(A) (a "public water system" is a system that "has at least fifteen service connections or regularly serves at least twenty-five individuals"). Therefore, exposures to these chemicals in drinking water from private wells is not addressed by the SDWA and need to be evaluated in the draft risk evaluation.

Moreover, the problem formulations themselves establish that exposures through drinking water persist for these chemicals despite any regulations under the SDWA, and it is arbitrary and capricious for EPA to ignore those exposures. For EPA to treat these exposure levels as "zero" when they are known not to be does not comport with the best available science. In particular, the problem formulations acknowledge that both perchloroethylene and trichloroethylene are common contaminants of ground water, surface water, and drinking water. It is particularly arbitrary and capricious to ignore exposures that are known to be common and potentially a significant source of risk.

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[11] Six-Year Review 2 of Drinking Water Standards, https://www.epa.gov/dwsixyearreview/six-year-review-2-drinking-water-standards#summary-table (last visited Jul. 31, 2018).

[12] Elsewhere, EPA indicates that carbon tetrachloride, methylene chloride, perchloroethylene, trichloroethylene (plus four more chemicals), were not included in the third six-year review because "these chemicals are being evaluated as part of the Group Regulation of Carcinogenic Volatile Organic Compound." U.S. EPA, *The Analysis of Regulated Contaminant Occurrence Data from Public Water Systems in Support of the Third Six-Year Review of National Primary Drinking Water Regulations: Chemical Phase Rules and Radionuclides Rules* at 1-1 (Dec. 2016), https://www.regulations.gov/document?D=EPA-HQ-OW-2016-0627-0147. However, the development of a group NPDWR for Carcinogenic Volatile Organic Compounds (VOCs) is in long-term action under EPA's Spring 2018 Regulatory Agenda. https://resources.regulations.gov/public/custom/jsp/navigation/main.jsp (last visited Jul. 30, 2018) (select "Environmental Protection Agency" and search for "volatile organic compound").

[13] PRIVATE DRINKING WATER WELLS, https://www.epa.gov/privatewells (last visited Jul. 31, 2018) (citing the US Census American Housing Survey 2015).

[14] An estimated 44.5 million people in the United States, or 14 percent of the population, provided their own water for domestic use in 2010. U.S. Geological Survey, *Estimated Use of Water in the United States in 2010* (2014), https://pubs.usgs.gov/circ/1405/pdf/circ1405.pdf.

For asbestos: Some U.S. drinking water supplies may contain 10-300 million asbestos fibers per liter. Problem Formulation for Asbestos at p. 29.

For carbon tetrachloride: 118 water systems reported mean concentrations of carbon tetrachloride greater than the Minimum Reporting Level (MRL) of 0.5 µg/L, which EPA's Office of Water has determined is the level showing a meaningful opportunity to improve public health. Problem Formulation for Carbon Tetrachloride at p. 35. The U.S. Geological Survey has also detected carbon tetrachloride in community water systems. *Id*.

For methylene chloride: EPA reported that methylene chloride has been detected in ground water and surface water, "including finished drinking water, through varied national monitoring efforts and water quality databases." Problem Formulation for DCM at p. 36. "Data compiled between 1992 and 2001 from NAWQA showed methylene chloride to be found in 6% of all ground water and surface water samples, with occurrences more common in surface water." *Id*.

For perchloroethylene: EPA acknowledged that "Perchloroethylene is a common contaminant in municipal drinking water supplies and ground water." Problem Formulation for Perchloroethylene at p. 41. "The general population may ingest perchloroethylene via contaminated drinking water, ground water and/or surface water." *Id*. at 46. Perchloroethylene contamination in U.S. surface water and ground water has been reported in 19.6% of samples and at 13.2% of sites, with detection in surface water occurring more frequently than in ground water. *Id*. at 41. Indeed, thirty-six states reported drinking water systems with at least one detection above the MCL. *Id*. Thus, even if the MCL were sufficient, it is not being met for perchloroethylene.

For trichloroethylene: EPA acknowledged that it is "one of the most frequently detected organic solvents in U.S. ground water." Problem Formulation for TCE at p. 34. "TCE has been detected in drinking water systems through national and state-wide monitoring efforts." *Id*. EPA acknowledged that it had ample evidence of TCE in drinking water monitoring data, and EPA cannot rationally treat TCE exposure through drinking water as "zero" when EPA knows these exposures continue to occur.

Given evidence of real-world exposure, EPA must assess those exposures in its risk evaluations. EPA cannot rationally exclude them from analysis.

ii) EPA's failure to regulate 1,4-dioxane and N-methylpyrrolidone (NMP) in drinking water does not justify EPA's decision to ignore exposures through drinking water; EPA should analyze the real-world exposures.

EPA is excluding exposures to 1,4-dioxane and N-methylpyrrolidone (NMP) through drinking water on an even more irrational and illegal basis. Specifically, EPA has not yet established any regulatory standard for these two chemicals under the Safe Drinking Water Act. Instead, they are on the Contaminant Candidate List, which EPA acknowledges "is a list of *unregulated* contaminants that are known or anticipated to occur in public water systems and that may require regulation." Problem Formulation for 1,4-Dioxane at p. 43 (emphasis added); Problem Formulation for NMP at p. 49. By EPA's own

acknowledgement, there are likely exposures to these chemicals through drinking water systems and they remain unregulated.

This approach is unreasonable for the reasons given above, but in addition, EPA does not even have the fig-leaf that these chemicals are regulated under other statutes. Numerous additional steps would need to be taken to actually regulate these chemicals under SDWA, which have not been taken. The vague statement that the chemical is "currently being evaluated"—with no specification of what outcomes may result or any timeline for further action toward regulation—provides no basis for EPA's assertion that its risks are being "adequately assess[ed] and effectively manage[d]." Problem Formulation for 1,4-Dioxane at pp. 42-43. An agency cannot ignore ongoing, current exposures on the theory that the agency might regulate that exposure at some uncertain point in the future. If a regulation is not legally in-place and in-force, EPA cannot rationally give it any weight. Among other things, it would be arbitrary and capricious to consider speculative future regulations that have not been promulgated through rulemaking and do not yet have legal effect.

EPA also cannot reasonably assume that it will know whether a final regulation will be finalized or, if so, the final regulation's conditions, until it has entered into and completed the notice-and-comment process for the regulation. *See Nat'l Rest. Ass'n v. Solis*, 870 F. Supp. 2d 42, 50 (D.D.C. 2012) ("[C]omments received by the agency are expected to shape the outcome of a final rule."). "The whole rationale of notice and comment rests on the expectation that the final rules will be somewhat different and improved from the rules originally proposed by the agency." *Trans-Pac. Freight Conf. of Japan/Korea v. Fed. Mar. Comm'n*, 650 F.2d 1235, 1249 (D.C. Cir. 1980). Thus, EPA cannot assume that any (entirely speculative) future MCL would provide adequate protection.

Moreover, the data in the problem formulations establishes that exposures through drinking water to 1,4-dioxane are likely and a cause for concern. As a factual matter, these exposures are occurring and EPA must consider them. With respect to NMP, it appears that EPA needs to perform further analysis regarding whether exposures are factually likely through drinking water.

For 1,4-dioxane: Of the 4,915 water systems monitored, 1,077 systems had detections of 1,4-dioxane in at least one sample. Problem Formulation for 1,4-Dioxane at p. 43. "341 systems (6.9%) had results at or above 0.35 µg/L (which corresponds to a 1 in a million-lifetime cancer risk)." *Id*. "Reported levels of 1,4-dioxane in groundwater range from 3 to 31,000 µg/L (ATSDR, 2012; USGS, 2002)." *Id*. at 28. EPA also acknowledged that some studies report 1,4-dioxane in surface water, though data are more limited and further study of surface water levels seems appropriate. *Id*. To ignore drinking water exposure when 1,4-dioxane has often been reported at hazardous levels is fundamentally arbitrary and capricious and a threat to public health.

iii) EPA needs to obtain actual data on potential exposure to HBCD, Pigment Violet 29, and 1-BP through drinking water exposures.

For the remaining three chemicals, EPA has included the drinking water pathway within the risk evaluation but has also insisted that it will perform no further analysis. See Problem Formulation for HBCD at pp. 51-52; Problem Formulation for PV 29 at p. 32; Problem Formulation for 1-BP at p. 53.

Instead, EPA provided at most a page's worth of analysis of this entire pathway for each chemical, and the resulting analysis largely fails to establish that EPA has sound reasons for failing to analyze this exposure pathway further.

First, EPA acknowledges that it has almost no data to justify these aspects of its analysis. See Problem Formulation for HBCD at pp. 51-52 ("Drinking water monitoring data is generally unavailable."); Problem Formulation for PV 29 at pp. 23, 32; Problem Formulation for 1-BP at p. 53 ("[T]here is no data of 1-BP found in US drinking water."). While EPA relies on the physical-chemical properties of these chemicals to estimate that concentrations of these chemicals in water are low, EPA has not established that these concentrations and exposures will not be significant, particularly in conjunction with other exposure pathways. EPA should use its available information authorities to fill these information gaps rather than assume "zero" exposure, particularly since EPA's analyses at best establish that the exposure levels may be low, not nonexistent.

Second, with respect to HBCD, EPA's analysis seems inconsistent with its earlier discussion of HBCD in the environment. "HBCD has been detected in a wide variety of environmental media." Problem Formulation for HBCD at p. 35. "HBCD is *** expected to be present in ambient air, indoor air and surface water." *Id*. EPA also acknowledges that "[t]he general population including populations living near industrial and commercial facilities processing, using or disposing of HBCD may be exposed by incidental ingestion of surface water and suspended particulates and by ingestion of HBCD from uptake (via direct or indirect deposition into water bodies or soil) from the environment into food sources." *Id*. at 50. Given widespread detections of HBCD in the environment, including surface water, it is arbitrary and capricious for EPA to assume low exposures through drinking water based on a lack of drinking water monitoring data. EPA also argues that it can ignore these exposures because the contribution of exposure is "expected to be low compared to other exposures," *id*. at 52, but without more analysis, EPA cannot conclude that those lower exposures are not significant, particularly when analyzed in combination with other exposures to HBCD. Even assuming EPA has established that other exposures are likely to be more significant, EPA has not established that EPA does not need to analyze how drinking water exposure may add to the overall risk.

E. Real-world exposures still occur through ambient water, and EPA cannot ignore those real-world exposures when assessing the risk to human health presented by a chemical substance.

Based on numerous rationales, EPA decided to effectively ignore all risks to human health arising from exposures through ambient water for nine of the ten chemicals.[15] The systematic decision to ignore the vast majority of exposures through this pathway is arbitrary and capricious because the available evidence reveals that exposures do occur through this pathway.

[15] EPA has correctly recognized that it must still analyze human exposures through ambient water from HBCD. *See* Problem Formulation for HBCD at p. 51.

i) The existence of a recommended water quality criterion for human health does not result in zero exposures to asbestos, carbon tetrachloride, methylene chloride, perchloroethylene, and trichloroethylene through ambient water; EPA should analyze the real-world exposures.

In discussing its approach to assessing risk to human health, EPA states it will exclude exposures to asbestos, carbon tetrachloride, methylene chloride, perchloroethylene, and trichloroethylene through ambient water because, under the Clean Water Act (CWA), EPA has recommended water quality criteria for protection of human health which are available for adoption into state water quality standards and to permitting authorities. See Problem Formulation for Asbestos at p.43; Problem Formulation for Carbon Tetrachloride at p. 49; Problem Formulation for DCM at p. 55; Problem Formulation for Perchloroethylene at pp. 60-61; Problem Formulation for TCE at pp. 54-55.

This approach is unreasonable for the reasons give above, but in addition, EPA has not made the necessary showing that the recommended water quality criteria it has set eliminate any unreasonable risk and EPA has not assessed all relevant aspects of the risk. Indeed, EPA has not even established or shown that these recommended water quality criteria meet EPA's illegal standard that these criteria "adequately assess and effectively manage exposures."

1) EPA has not addressed several reasons that its Clean Water Act authority is not a comprehensive substitute for action under TSCA.

Under the Clean Water Act (CWA), EPA establishes recommended water quality criteria, but not all states have updated their criteria to reflect the current CWA criteria. *See* 80 Fed. Reg. 36,986 (June 29, 2015). There is often significant variation between EPA's recommended criteria (shown in the table below) and the criteria adopted by the states.

EPA's National Recommended Water Quality Criteria for Four of the First Ten Chemicals:[16]

Chemical Name	**Human Health Criteria for w+o (µg/L)**	**Human Health Criteria for o (µg/L)**
TCE	0.6	7
Carbon tetrachloride	0.4	5
Perchloroethylene	10	29
Methylene chloride	20	1,000

[16] There are two sets of human health criteria: (1) exposure through organisms only (o), and (2) exposure to water and organisms (w+o). NATIONAL RECOMMENDED WATER QUALITY CRITERIA - HUMAN HEALTH CRITERIA TABLE, https://www.epa.gov/wqc/national-recommended-water-quality-criteria-human-health-criteria-table.

For example, Illinois has set its human health criteria for TCE at 25 µg/L and has no human health criteria for perchloroethylene.[17] Maryland has set its human health criteria for TCE, carbon tetrachloride, and methylene chloride at higher levels than the current EPA recommended water quality criteria.[18] Other examples of states adopting less stringent standards are available. Given that some states have water quality criteria that are significantly less protective than EPA's recommendations, EPA cannot rely on its recommendations to assume that the risks are adequately managed, much less that they result in zero exposure.

EPA has also not assessed whether the established criteria, which EPA set and were adopted to varying extents by states in the past, reflect the current best available science regarding the risk presented by these chemicals. For example, EPA acknowledges that EPA may need to update its water quality criteria for some of these chemicals (though, inexplicably, not for others). *See, e.g.*, Problem Formulation for Carbon Tetrachloride at p. 49 ("EPA may update its CWA section 304(a) water quality criteria for carbon tetrachloride in the future under the CWA."); Problem Formulation for DCM at p. 55.

Moreover, while EPA relies on the CWA to dismiss the entire ambient water pathway, EPA never acknowledges the ongoing uncertainty surrounding the definition of "waters of the United States"[19] regulated under the CWA. EPA itself has stated that since the Supreme Court's decision in *Rapanos v. United States*, 547 U.S. 715 (2006), there has been uncertainty regarding the regulatory reach of the CWA. The EPA Office of Inspector General has stated that "*Rapanos* has created a lot of uncertainty with regards to EPA's compliance and enforcement activities. Processing enforcement cases where there is a jurisdictional issue has become very difficult."[20] EPA cannot assume that all ambient water is adequately managed under the CWA when EPA itself expresses ongoing uncertainty over the jurisdictional reach of the CWA.

Indeed, EPA has asserted that *Solid Waste Agency of Northern Cook County v. Army Corps of Engineers*, 531 U.S. 159 (2001), "squarely eliminate[d] CWA jurisdiction over isolated waters that are intrastate and non-navigable, where the sole basis for asserting CWA jurisdiction is the actual or potential use of the waters as habitat for migratory birds that cross state lines in their migrations." Advance Notice of Proposed Rulemaking on the Clean Water Act Regulatory Definition of "Waters of the United States," 68

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[17] DERIVED WATER QUALITY CRITERIA, http://www.epa.illinois.gov/topics/water-quality/standards/derived-criteria/index (last visited Aug. 16, 2016).

[18] NUMERICAL CRITERIA FOR TOXIC SUBSTANCES IN SURFACE WATERS, http://www.dsd.state.md.us/comar/comarhtml/26/26.08.02.03-2.htm (last visited Aug. 16, 2018).

[19] EPA's main webpage summarizes the ongoing litigation regarding the 2015 regulation that finalized a definition of "waters of the United States." *See* ABOUT WATERS OF THE UNITED STATES, https://www.epa.gov/wotus-rule/about-waters-united-states (last visited Aug. 11, 2018).

[20] U.S. EPA, Office of Inspector General, *Congressionally Requested Report on Comments Related to Effects of Jurisdictional Uncertainty on Clean water Act Implementation* (Apr. 2009), https://www.epa.gov/sites/production/files/2015-11/documents/20090430-09-n-0149.pdf.

Fed. Reg. 1991, 1996 (Jan. 15, 2003). Therefore, it makes even less sense that EPA would assume that the CWA will ensure that all ambient waters are adequately managed.

Furthermore, EPA cannot assume that the CWA has adequately managed the discharge of all these chemicals because there are recognized lapses in the regulatory process. EPA's Office of Inspector General has reported that:

> Management controls put in place by the EPA to regulate and control hazardous chemical discharges from sewage treatment plants to water resources have limited effectiveness. The EPA regulates hazardous chemical discharges to and from sewage treatment plants, but these regulations are not effective in controlling the discharge of hundreds of hazardous chemicals to surface waters such as lakes and streams. Sewage treatment plant staff do not monitor for hazardous chemicals discharged by industrial users.[21]

At the time of the report by the Inspector General, there was no database of the information submitted by dischargers, nor was a compilation of the information available to officials in the regions or states that were interviewed.

Considering the documented lack of awareness regarding chemical discharges into and out of wastewater treatment plants, and EPA's own acknowledged failure to regulate discharges through this pathway, EPA should commit to analyzing any exposures through this pathway in its risk evaluations.

In sum, EPA has failed to analyze numerous aspects of its exercise of its CWA authority that amply demonstrate that EPA cannot dismiss the entire ambient water pathway simply because EPA has established water quality criteria. EPA must analyze the ambient water pathway in the risk evaluations.

2) *The problem formulations contain information establishing that there is exposure through ambient water.*

In any event, the recommended water quality criteria clearly do not eliminate exposures. As EPA itself acknowledges in the problem formulations, discharges are still permissible for these chemicals. *See, e.g.*, Problem Formulation for Perchloroethylene at p. 121 ("Perchloroethylene may also be discharged to waterways if proper permits are held."). A number of the problem formulations cite evidence of the presence of the chemicals in ambient water as well as drinking water:

For asbestos: EPA has evidence of asbestos in drinking water supplies, as described above, and EPA also has evidence that "asbestos has been detected in many different freshwater fishes and mussels from bodies of water contaminated with asbestos." Problem Formulation for Asbestos at p. 29.

[21] U.S. EPA, Office of Inspector General, *More Action is Needed to Protect Water Resources from Unmonitored Hazardous Chemicals* at 3 (Sept. 2014), https://www.epa.gov/sites/production/files/2015-09/documents/20140929-14-p-0363.pdf.

For carbon tetrachloride: EPA has evidence of carbon tetrachloride bring widespread in the environment and in drinking water supplies. See Problem Formulation for Carbon Tetrachloride at p. 35. EPA should assess whether the data reveal carbon tetrachloride being widespread in ambient water as well.

For methylene chloride: EPA acknowledges that methylene chloride is detected in surface water. Problem Formulation for DCM at p. 36. EPA cannot assume that methylene chloride has nonexistent exposure through ambient water when the data show it is present.

For perchloroethylene: "Perchloroethylene has been found in air, soil, surface water, salt water, drinking water, aquatic organisms and terrestrial organisms." Problem Formulation for Perchloroethylene at p. 40. EPA reports that perchloroethylene contamination of drinking water and ground water is common. Perchloroethylene was detected in surface water and ground water in 19.6% of samples, with surface water contamination being more common than ground water exposure. *Id.* at 41. With evidence of widespread water contamination, EPA cannot rationally ignore exposures to perchloroethylene through ambient water.

For trichloroethylene: EPA reported detections in surface water at a maximum of 50 ppb and average of 4.5 ppb. Problem Formulation for TCE at p. 34. An average of 4.5 ppb is not zero, and EPA should consider how this exposure may combine with exposures from other pathways to assess the overall risk from TCE.

EPA should look to the real-world exposures for these chemicals to assess their risk. The problem formulations provide relatively little information about the monitoring results for these chemicals in surface water. EPA should examine and summarize that exposure information when evaluating the risks presented by these chemicals; if that information is insufficient, EPA should use its authorities to require the development of additional needed information.

ii) EPA's failure to regulate 1,4-dioxane under the Clean Water Act does not justify EPA's decision to ignore exposures through ambient water; EPA should analyze the real-world exposures.

EPA is excluding exposures to 1,4-dioxane through ambient water on an even more irrational and illegal basis. *See* Problem Formulation for 1,4-Dioxane at pp. 43-44. EPA discusses the issue of a water quality criterion for 1,4-dioxane, but EPA never acknowledges that it has not yet set a human health criterion for 1,4-dioxane.[22] As EPA itself later admits in the problem formulation, only a single state has developed a water quality standard for human health for 1,4-dioxane. *See, e.g.*, Problem Formulation for 1,4-Dioxane at pp. 44 ("Currently, only one state (Colorado) includes human health criteria for 1,4-

[22] *See* NATIONAL RECOMMENDED WATER QUALITY CRITERIA - HUMAN HEALTH CRITERIA TABLE, https://www.epa.gov/wqc/national-recommended-water-quality-criteria-human-health-criteria-table (last visited Aug. 16, 2018).

dioxane in their water quality standards."). EPA's failure to regulate 1,4-dioxane under the CWA cannot justify EPA's decision to exclude this pathway, for reasons previously articulated in Section 5.D.ii.

Moreover, the factual record establishes that 1,4-dioxane is present in water sources, and EPA should use its information authorities to obtain needed additional information about its presence in ambient water. EPA has evidence of 1,4-dioxane in drinking water supplies, as described above, and evidence of 1,4-dioxane in groundwater. Problem Formulation for 1,4-Dioxane at p. 28. EPA has acknowledged that it has "relatively fewer data available on 1,4-dioxane in surface water," so EPA should use its information authorities to obtain more data. *Id*.

iii) EPA needs to obtain actual data on potential exposure to NMP, Pigment Violet 29, and 1-BP through ambient water exposures.

For the remaining three chemicals, EPA included the ambient water pathway within the risk evaluation but also insisted that it would perform no further analysis. *See* Problem Formulation for NMP at p. 47; Problem Formulation for PV 29 at p. 32; Problem Formulation for 1-BP at p. 53. Instead, once again, EPA provided at most a page's worth of analysis of this pathway for each chemical, and the resulting analysis largely fails to establish that EPA has sound reasons for failing to analyze this exposure pathway further.

As with drinking water, EPA acknowledges that it has almost no data to justify this aspect of its analysis. *See* Problem Formulation for NMP at p. 47 ("Environmental monitoring data were not identified for NMP."); Problem Formulation for PV 29 at p. 23 ("EPA did not find environmental monitoring data (e.g., presence in air, soil, sediment, surface water, or biota)"); *see also* Problem Formulation for 1-BP at p. 34. While EPA invokes the physical-chemical properties of these chemicals to declare that concentrations of these chemicals in water are low, EPA has not established that these concentrations and exposures will not be significant, particularly in conjunction with other exposure pathways. EPA should use its available information authorities to fill these information gaps rather than assume low exposure.

For example, in the absence of any actual monitoring data for NMP, EPA conducted a questionable "first-tier exposure analysis." Problem Formulation for NMP at p. 47. *See* Section 47.A.ii for detail on concerns about this first-tier analysis. While EPA suggests that these predicted exposures, standing alone, would not likely present a risk, EPA should consider whether these exposures could present a risk when combined with exposures through other sources, such as air and other exposures EPA intends to exclude, as well as the exposures that EPA is analyzing through the risk evaluations.

F. Real-world exposures still occur through disposal pathways, and EPA cannot ignore those real-world exposures when assessing the risk presented by a chemical substance.

For every chemical substance except Pigment Violet 29,[23] EPA contends that due to regulation of disposal under the Resource Conservation and Recovery Act (RCRA), the Clean Air Act (CAA), the Safe

[23] While EPA retains the disposal pathway for Pigment Violet 29, EPA gives it an incredibly cursory analysis and intends not to analyze it further, relying on the "design standards for Subtitle-D lined landfills" and expectations about its tendency to leach. *See* Problem Formulation for PV 29 at p. 33. EPA

Drinking Water Act (SDWA), and various state programs, EPA can ignore all exposures from all disposal-related pathways and associated activities (e.g., collection, processing, storage and transport). Problem Formulation for Asbestos at pp. 43-44; Problem Formulation for 1-BP at pp. 54-55; Problem Formulation for 1,4-Dioxane at pp. 44-45; Problem Formulation for Carbon Tetrachloride at pp. 50-51; Problem Formulation for HBCD at pp. 52-53; Problem Formulation for DCM at pp. 55-57; Problem Formulation for NMP at pp. 50-51; Problem Formulation for Perchloroethylene at pp. 61-63; Problem Formulation for TCE at pp. 55-56.

This approach is unreasonable for the reasons given above. EPA has not made the necessary showing that these regulations eliminate any unreasonable risk and EPA has not assessed all relevant aspects of the risk. Indeed, EPA has not even established or shown that these disposal regulations meet EPA's illegal standard that these regulations "adequately assess and effectively manage exposures." For example, EPA has not shown or established that disposal in a RCRA Subtitle C hazardous waste landfill or a RCRA Subtitle D non-hazardous waste landfill would actually reduce unreasonable risk to a sufficient extent. EPA's approach is also arbitrary and capricious for a variety of reasons.

With respect to asbestos, 1-BP, HBCD, and methylene chloride, the problem formulations indicate that the chemical is not listed as a hazardous waste under RCRA. Problem Formulation for Asbestos at p. 43 ("Asbestos is not regulated as a RCRA hazardous waste under RCRA Subtitle C."); Problem Formulation for 1-BP at p. 92 ("Currently, 1-BP is not regulated under federal regulations as a hazardous waste."); Problem Formulation for HBCD at pp. 52-53 ("HBCD is not classified as a RCRA hazardous waste."); Problem Formulation for NMP at pp. 50-51 (not referring to any listing). EPA cannot rely on the RCRA regulatory regime as a basis for ignoring exposures under TSCA when EPA has not even issued a regulatory decision under RCRA for these chemicals.

Moreover, while EPA invokes the standards for RCRA Subtitle C landfills as providing sufficient protection, not all disposal occurs in such landfills. For example, EPA acknowledges that the majority of asbestos land disposal does not occur in RCRA Subtitle C landfills. Problem Formulation for Asbestos at pp. 43-44. Similarly, for NMP, the vast majority of off-site releases to land (~2.7 million pounds in 2016) went to landfills other than RCRA Subtitle C landfills. Problem Formulation for NMP at pp. 50-51. Even chemicals allegedly managed under RCRA can be or are disposed of in non-hazardous waste landfills. For example, EPA's TRI reporting on 1-BP showed that most of the releases to the land were to "other off-site landfills," not RCRA Subtitle C landfills. Problem Formulation for 1-BP at p. 34. EPA cannot rely on regulations that do not apply to protect against risks.

Even for those chemicals regulated under RCRA, EPA acknowledges that disposal also occurs in Subtitle D municipal solid waste (MSW) landfills and industrial-non-hazardous and construction/demolition waste landfills (which are primarily regulated under state regulatory programs). These disposal approaches do not need to meet the requirements of Subtitle C landfills, thus EPA's invocation of the Subtitle C standards does not justify ignoring exposures from these disposals. While the purpose of

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should obtain some actual monitoring and testing information to assess whether its conclusion is accurate.

RCRA subtitle C is at least to "protect human health and the environment," *see, e.g.*, 42 U.S.C. §§ 6922(a), 6924(a), subtitle D is intended "to assist in developing and encouraging methods for the disposal of solid waste which are environmentally sound and which maximize the utilization of valuable resources including energy and materials *** and to encourage resource conservation." 42 U.S.C. § 6941. Therefore, EPA's exclusions based on the regulations under subtitle D potentially raise even greater, unaddressed, public health concerns than EPA's exclusions under subtitle C.

In addition, states impose varying requirements on such landfills under their delegated RCRA Subtitle D authorities. For example, EPA indicates that some state programs may not include requirements for liners to limit release of landfill leachate.

EPA itself has acknowledged that enforcement and regulation under RCRA is inconsistent, so EPA cannot simply assume that RCRA implementation provides a basis for ignoring exposures under TSCA. As the Office of Inspector General explained the challenges of the RCRA system:

> The Hazardous and Solid Waste Amendments of 1984 (HSWA) amended RCRA and added provisions including land disposal restrictions, RCRA corrective action for solid waste management units and regulation of small-quantity generators. When the EPA creates new hazardous waste rules, it does so under the authority of either or both of these laws. Rules promulgated under HSWA authority are immediately effective in all states and are administered by the EPA until states become authorized for those rules. In contrast, *rules promulgated under RCRA authority (non-HSWA rules) cannot be enforced by the EPA in states with an authorized base program and do not go into effect until these states become authorized for the rules.*[24]

According to the OIG, the fact that a number of rules are not yet adopted by the states and cannot be enforced by EPA "creates a regulatory gap and risk to human health and the environment, and an inconsistent regulatory landscape across the states."[25] OIG's report states that "there are almost 1,300 instances of required rules for which various state hazardous waste programs have not been authorized. Of the rules for which states have not received authorization, there are about 500 each of HSWA and non-HSWA rules, and about 300 rules that have components of both."[26]

When states do not keep their hazardous waste programs up to date, it means citizens in different states are unevenly protected from hazardous waste-related risks. This is critical because "60,000 RCRA facilities exist in the United States, generating and managing 30 to 40 million tons of hazardous waste

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[24] U.S. EPA, Office of Inspector General, *Incomplete Oversight of State Hazardous Waste Rule Authorization Creates Regulatory Gaps and Human Health and Environmental Risks* at 2 (Jul. 2018), https://www.epa.gov/sites/production/files/2018-07/documents/_epaoig_20180731-18-p-0227.pdf (emphasis added).

[25] *Id.* at 11.

[26] *Id.* at 12; *see also* AUTHORIZATION STATUS BY RULE, https://www.epa.gov/sites/production/files/2018-06/documents/authorization_status_by_rule.pdf (last visited Aug. 10, 2018) (documenting for each state whether they have adopted the RCRA regulations).

annually. Eighty percent of all U.S. citizens live within a 3-mile radius of a RCRA-regulated hazardous waste generator or treatment storage and disposal facility, and 50 percent of citizens live within a 1-mile radius."[27] Therefore, EPA cannot rely on any assumption of consistent implementation and enforcement of RCRA to ensure that all exposures have been adequately managed.

Indeed, many of the problem formulations themselves establish that exposures from disposal persist for these chemicals despite RCRA regulations, and it is arbitrary and capricious for EPA to ignore those exposures. For EPA to treat these exposure levels as "zero" when they are known to exist does not comport with the best available science.

To be sure, EPA often appears to have less monitoring information that speaks to whether a particular exposure arises from disposal or some other source, and EPA also appears to have less monitoring information about these chemicals' presence in soil, sediment, and leachate, than it does for their presence in water or air. *See, e.g.*, Problem Formulation for TCE at p. 34 ("Compared with other environmental media, there is a relative lack of nationally representative monitoring data on levels of TCE in ambient soil."). As EDF has previously explained, EPA must consider "reasonably available" information, and thus EPA must both consider the information it already possesses and use its authorities under TSCA §§ 4 and 8 to obtain additional information. EDF incorporates and reiterates those points here as well.[28] EPA should use those authorities to obtain additional information about the exposures arising from disposal for these chemicals.

EPA cannot assume that exposure from disposal is zero just because it could be regulated under other authorities. For example, the problem formulations contain information suggesting that exposures may arise from disposal. In particular, as detailed below, asbestos appears in sewage sludge, and EPA has data showing that 1,4-dioxane, HBCD, methylene chloride, NMP, and trichloroethylene are present in landfill leachate, despite the various regulations that allegedly render these exposures insignificant.

For asbestos: EPA acknowledged that "[a]sbestos fibers can be found in soils, sediments, lofted in air and windblown dust, surface water, ground water and biota." Problem Formulation for Asbestos at p. 26. "Asbestos fibers have been measured in U.S. municipal sewage sludges, with asbestos fiber content up to 10% of ashed sludge by volume." *Id*. at 29.

For 1,4-dioxane: EPA acknowledges that "1,4-Dioxane has also been detected in landfill leachate." Problem Formulation for 1,4-Dioxane at p. 28.

For HBCD: "There may be releases of HBCD from industrial sites to wastewater treatment plants (WWTP), surface water, air and landfill." Problem Formulation for HBCD at p. 34. "Disposal of EPS and XPS foam may result in releases to the environment as a result of demolition of buildings or material

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[27] U.S. EPA, Office of Inspector General, *EPA Has Not Met Statutory Requirements for Hazardous Waste Treatment, Storage and Disposal Facility Inspections, but Inspection Rates Are High* at 1 (March 2016), https://www.epa.gov/sites/production/files/2016-03/documents/20160311-16-p-0104.pdf.

[28] EDF Comments on Ten Scopes under the Toxic Substances Control Act pp.11-15, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069.

that is left on or in the soil." *Id.* "Articles that contain HBCD may release HBCD to the environment during use or through recycling and disposal." *Id*. at 35. "HBCD has been widely detected in both the environment and biota." *Id*. at 35. "HBCD is expected to be present at relatively higher levels in sediment, soil and indoor dust." *Id*. "HBCD has been detected in leachate and HBCD containing materials are sent to landfill as part of disposal." *Id*. at 103.

For methylene chloride: EPA acknowledges that various studies and databases provide hundreds of measurements of methylene chloride in soil and sediment. Problem Formulation for DCM at p. 36. "In a literature review of various VOC concentrations found in landfill leachates, Klett et al. (2005) found methylene chloride ranged in concentration from 1.0 – 58,200 µg/L. Staples et al. (1985) reported that methylene chloride was found in 20% of sediment samples in the STORET database." *Id*. at 36-7.

For NMP: "NMP has been detected in industrial landfill leachate." Problem Formulation for NMP at p. 33. "NMP has been detected in wastewater." *Id*.

For perchloroethylene: "Perchloroethylene has been found in air, soil, surface water, salt water, drinking water, aquatic organisms and terrestrial organisms. Historic industrial, commercial and military use of perchloroethylene, including unregulated or improper disposal of perchloroethylene wastes, has resulted in location-specific soil and ground water contamination." Problem Formulation for Perchloroethylene at p. 40.

For trichloroethylene: "TCE is widely detected in a number of environmental media. *** TCE is frequently found at Superfund sites as a contaminant in soil and ground water." Problem Formulation for TCE at p. 33.

G. Real-world exposures still occur through biosolids pathways, and EPA cannot ignore those real-world exposures when assessing the risk presented by a chemical substance.

Based on numerous rationales, EPA decided to effectively ignore all risks arising from exposures through biosolids for at least seven of the ten chemicals (EPA's problem formulations are unclear about how it will consider biosolids for two of them).[29] The systematic decision to ignore the vast majority of exposures through this pathway is arbitrary and capricious because the available evidence reveals that exposures do occur through this pathway for at least three of these chemicals.

[29] EPA has correctly recognized that it must still analyze exposures through biosolids for HBCD. *See* Problem Formulation for HBCD at p.51. EPA is unclear in its discussion of biosolids and 1,4-dioxane. *Compare* Problem Formulation for 1,4-Dioxane at p. 9 ("EPA plans to include surface water exposure to aquatic vertebrates, invertebrates and aquatic plants, exposure to sediment organisms and exposure to 1,4- dioxane in land-applied biosolids in the risk evaluation."), *with id.* at 42 ("EPA does not plan to further analyze other releases to land during risk evaluation, including biosolids application to soil."). EPA provides a cursory analysis of biosolids for Pigment Violent 29 but then states that "land application of biosolids *** is outside of scope of this assessment." Problem Formulation for PV 29 at p. 33.

i) EPA cannot ignore known exposures from biosolids for carbon tetrachloride and perchloroethylene on the theory that EPA may someday regulate them under CWA Section 405(d).

In the problem formulations, EPA acknowledges that its sewage surveys and biennial reviews for biosolids have identified carbon tetrachloride and perchloroethylene as toxic chemicals occurring in biosolids. Problem Formulation for Carbon Tetrachloride at p. 49; Problem Formulation for Perchloroethylene at p. 61. Given the known presence of these chemicals in biosolids and the potential for exposure, EPA must analyze these exposures when assessing whether these chemicals present an unreasonable risk.

EPA states that it will disregard these exposures because "EPA can potentially regulate those pollutants under CWA 405(d), based on a subsequent assessment of risk. EPA's Office of Water is currently developing modeling tools in order to conduct risk assessments for chemicals in biosolids. Because the biosolids pathway for [these chemicals are] currently being addressed in the CWA regulatory analytical process, this pathway will not be further analyzed in the risk evaluation." *See, e.g.*, Problem Formulation for Perchloroethylene at p.61. On its face, these statements are contradictory and irrational. EPA admits that the pathways are not yet being addressed, and the relevant office has not even developed models to address these pathways. EPA cannot rationally exclude a known pathway of exposure under TSCA because EPA "can potentially" regulate that pathway through a different mechanism at some unknown date in the future.

As explained above in Section 5.D.ii, if a regulation is not legally in-place and in-force, EPA cannot rationally give it any weight. Among other things, it would be arbitrary and capricious to consider speculative future regulations that have not been promulgated through rulemaking and do not yet have legal effect.

ii) EPA knows of evidence that asbestos is present in biosolids, so EPA must analyze this pathway of exposure.

The problem formulation for asbestos acknowledges that asbestos has been detected in biosolids in the United States. *See* Problem Formulation for Asbestos at p. 29. "EPA has identified literature which indicates that asbestos has been detected in biosolids from municipal wastewater treatment." *Id*. at 42. EPA asserts, without explanation, that it is expected that concentrations of asbestos in biosolids will be low. *Id*. But EPA provides no evidence supporting the conclusion that the concentrations will be low. In addition, asbestos is a particularly hazardous substance, so even low concentrations of asbestos may present an unreasonable risk. Without further analysis and evidence, EPA cannot simple assume that asbestos' presence in biosolids will not present an unreasonable risk.

iii) EPA should obtain some actual monitoring data to confirm its biosolids predictions for 1-BP, 1,4-dioxane, methylene chloride, NMP, and TCE, and to the extent EPA excludes biosolids on the theory that the chemical will instead enter other pathways, EPA must consider those exposure pathways.

For 1-BP, 1,4-dioxane, methylene chloride, NMP, and TCE, EPA states that these chemicals are expected to either enter the aqueous component and/or volatilize to air, and thus asserts EPA can ignore the biosolids exposure pathway. *See, e.g.*, Problem Formulation for 1-BP at pp. 53-54; Problem Formulation for 1,4-Dioxane at p. 42; Problem Formulation for DCM at p. 53; Problem Formulation for NMP at p. 48; Problem Formulation for TCE at pp. 53.

EPA should obtain some monitoring data to confirm these analyses, but in any event, EPA cannot rationalize ignoring exposures from biosolids on the basis that these chemicals will enter the water and air and then also choose to ignore the exposure pathways through water and air. EPA's justification for ignoring the biosolids pathways for these chemicals highlights that EPA's decision to ignore other pathways is particularly arbitrary and capricious.

iv) EPA needs to better explain its approach to Pigment Violet 29 and biosolids, and EPA should assess this exposure pathway more robustly than it has.

In contrast to the chemicals discussed above, EPA draws the opposite conclusion for Pigment Violet 29, emphasizing that because sorption to biosolids is expected to be strong, it can assume low levels of leaching (allowing EPA to rationalize its disregarding the drinking water and ambient water pathways), but then stating that "land application of biosolids is not expected to be a release pathway for the manufacturer, so this pathway is outside of scope of this assessment." Problem Formulation for PV 29 at p. 33. EPA's explanation in this cursory analysis is difficult to follow: EPA notes that the manufacturer of Pigment Violet 29 sends its sludge to a RCRA Subtitle D landfill, *id.*, but it is not clear why that would mean EPA can therefore disregard exposures from biosolids. Given Pigment Violet 29's expected presence in biosolids, EPA should analyze this pathway unless EPA has empirical evidence showing that it will not lead to exposures.

H. EPA must analyze all the environmental risks presented by asbestos, HBCD, methylene chloride, perchloroethylene, and trichloroethylene through ambient water.

EPA recognizes that it must evaluate the risks to aquatic species arising from exposures through water for asbestos, HBCD, methylene chloride, perchloroethylene, and trichloroethylene. Problem Formulation for Asbestos at p. 41; Problem Formulation for HBCD at pp. 50-51; Problem Formulation for DCM at p. 53; Problem Formulation for Perchloroethylene at p. 59; Problem Formulation for TCE at p. 53.

But EPA has not committed to analyzing the risks to terrestrial species from exposure through ambient water for any of these chemicals except HBCD, despite the fact that terrestrial species also can experience exposures through surface water. *But see* Problem Formulation for HBCD at p. 50 ("Aquatic and terrestrial ecological receptors may also be directly exposed due to proximity to surface water and sediment."). When EPA evaluates the risks presented by exposure through ambient water, EPA must consider the risks presented to terrestrial ecological receptors as well as aquatic species.

EPA provides no convincing explanation for excluding exposures to terrestrial or sediment-dwelling organisms for asbestos, methylene chloride, perchloroethylene, and trichloroethylene. For asbestos,

EPA acknowledges that once in water, asbestos will eventually settle into sediments, and that EPA is still reviewing the literature regarding the risk; EPA should not complete its evaluation of this risk until it has completed the literature review and can accurately establish that exposure levels through these media present no unreasonable risk. Problem Formulation for Asbestos at p. 42. For methylene chloride, EPA states it will not further analyze exposure to terrestrial organisms through water, sediment, or migration from biosolids via soil deposition, based on the argument that "[t]errestrial species exposures to MC in water are orders of magnitude below hazardous concentrations." (Appendix E, pp. 139-140) Yet it is far from clear how EPA arrived at this conclusion. *See* Section 43.A for further discussion. For perchloroethylene, EPA simply does not address terrestrial organisms' exposure to surface water (though EPA acknowledges it must analyze exposure to sediment-dwelling organisms). Problem Formulation for Perchloroethylene at p. 12. For trichloroethylene, EPA simply asserts that "physical chemical properties do not support an exposure pathway through water and soil pathways" to terrestrial organisms, but EPA provides no analysis of why this is so.

I. EPA cannot rely on its actions under other authorities when there are numerous problems with compliance, implementation, and enforcement under those authorities.

EPA cannot ignore exposure through these pathways for the reasons given above, but in addition, it is arbitrary and capricious for EPA to assume zero exposure through other pathways based on EPA-administered statutes when EPA has documented extensive problems with compliance, implementation, and enforcement of these statutes.

i) EPA's own analyses establish that State enforcement of these environmental statutes is inconsistent and often deficient.

There are multiple EPA reports documenting enforcement problems with EPA's environmental statutes.[30] Specifically, these reports have noted that "data quality, identification of violations, issuing enforcement penalties and other enforcement actions in a timely and appropriate manner, and general oversight issues" are all key issues impacting the enforcement of these statutes.[31]

Generally, EPA's regional offices provide oversight to ensure that the state enforcement programs are following EPA's guidance, policies, and regulations.[32] Despite EPA oversight, which is a separate concern, state enforcement of these statutes has been found deficient in a number of cases. For instance:

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[30] U.S. EPA, Office of Inspector General, *EPA Must Improve Oversight of State Enforcement* at App. B, p. 32-34 (Dec. 2011), https://www.epa.gov/sites/production/files/2015-10/documents/20111209-12-p-0113.pdf (identifying a long list of GAO and OIG reports documenting deficiencies in enforcement of environmental statutes).

[31] *Id.* at 32.

[32] U.S. Government Accountability Office, *EPA-State Enforcement Partnership Has Improved, but EPA's Oversight Needs Further Enhancement* at 1 (Jul. 2007), https://www.gao.gov/products/GAO-07-883.

- According to a 2011 OIG report, **North Dakota** appears "philosophically opposed to taking enforcement action."[33] For instance, during the entire period of the report (FYs 2003-2009), the state assessed no penalties against known CWA violators.[34]
- In **Louisiana** multiple petitions have been filed by citizens to remove the state's delegated authorities under the CWA, CAA, and RCRA.[35] The poor performance under these statues was attributed to "a lack of resources, natural disasters, and a culture in which the state agency is *expected to protect industry*."[36]
- The **U.S Virgin Islands** "has not met program requirements for numerous activities related to implementing the Clean Air Act, Clean Water Act, Safe Drinking Water Act, and Underground Storage Tank/Leaking Underground Storage Tank programs. These activities included monitoring environmental conditions, conducting compliance inspections and enforcing program requirements."[37]

Notably, even where enforcement of these statutes has been consistently deficient, EPA has generally not de-authorized states. According to the 2011 OIG report, "the threat of EPA revoking a state's authorization [is] moot because there is a general understanding that no EPA region has the resources to operate a state program. This reality undercuts EPA's strongest tool for ensuring that authorized states adequately enforce environmental laws: de-authorization."[38] Although EPA has taken steps in a number of cases to improve state programs, ultimately implementation and enforcement of these statutes remains deficient in a number of states, resulting in continued excessive exposure to these chemicals through air, water, and land. These exposures EPA must be assessed under TSCA.

Below are a few more specific examples, among many, of deficiencies under each of the statutes.

Safe Drinking Water Act: As explained above, EPA has excluded exposures to drinking water for several of the chemicals based on the assumed effectiveness of state implementation and enforcement of the SDWA. A 2011 GAO report states that EPA often receives unreliable data from the states.[39] EPA relies

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[33] U.S. EPA, Office of Inspector General, *EPA Must Improve Oversight of State Enforcement* at 17 (Dec. 2011), https://www.epa.gov/sites/production/files/2015-10/documents/20111209-12-p-0113.pdf.
[34] *Id.* at 15.
[35] *Id.* at 16.
[36] *Id.* (emphasis added).
[37] U.S. EPA, Office of Inspector General, *Conditions in the U.S. Virgin Islands Warrant EPA Withdrawing Approval and Taking Over Management of Some Environmental Programs and Improving Oversight of Others* (April 2015), https://www.epa.gov/sites/production/files/2015-09/documents/20150417-15-p-0137.pdf; U.S. EPA Region 2, *National Strategy Oversight Plan* at 3 (Mar. 2016), https://www.documentcloud.org/documents/2992740-Region-2-State-Oversight-Plan-March-2016-v2.html.
[38] U.S. EPA, Office of Inspector General, *EPA Must Improve Oversight of State Enforcement* at 17 (Dec. 2011), https://www.epa.gov/sites/production/files/2015-10/documents/20111209-12-p-0113.pdf.
[39] U.S. Government Accountability Office, *Unreliable State Data Limit EPA's Ability to Target Enforcement Priorities and Communicate Water Systems' Performance* (June 2011), https://www.gao.gov/products/GAO-11-381.

on state data to determine whether there is compliance with the SDWA. Without reliable data EPA has no way to verify that the requirements of the SDWA are being met by the states.

Here is one example of deficient state enforcement of the SDWA:

- **Pennsylvania**: EPA sent a letter in December 2016 to the Pennsylvania Department of Environmental Protection, stating that the department lacks the necessary staff to enforce safe drinking water standards and that the lack of staff has caused the number of unaddressed Safe Drinking Water Act violations to nearly double in the past five years, from 4,298 to 7,922.[40]

Clean Water Act: EPA has also excluded exposures to ambient water for numerous chemicals based on the assumed "effectiveness" of the CWA's National Pollution Discharge Elimination System (NPDES) program and the water quality criteria process.

But over half of assessed U.S. river and stream miles violate state water quality standards.[41] EPA's own analysis, provided below, indicates that waters remained impaired throughout the United States, despite the CWA standards.

Assessed Water of the United States[42]

	Size of Water							
	Rivers and Streams (Miles)	Lakes, Reservoirs, and Ponds (Acres)	Bays and Estuaries (Square Miles)	Coastal Shoreline (Miles)	Ocean and Near Coastal (Square Miles)	Wetlands (Acres)	Great Lakes Shoreline (Miles)	Great Lakes Open Water (Square Miles)
Good Waters	516,800	5,392,817	11,516	1,285	617	569,328	106	1
Threatened Waters	4,495	30,309						
Impaired Waters	586,910	13,158,111	44,619	3,330	6,218	665,979	4,354	39,230
Total Assessed Waters	1,108,205	18,581,237	56,135	4,615	6,836	1,235,307	4,460	39,231
Total Waters	3,533,205	41,666,049	87,791	58,618	54,120	107,700,000	5,202	196,343
Percent of Waters Assessed	31.4	44.6	63.9	7.9	12.6	1.1	85.7	20.0

EPA also publishes the Annual Noncompliance Report, which summarizes enforcement data for facilities with individual NPDES permits but that are not major dischargers.[43] According to the 2015 report, the percentage of facilities with formal enforcement actions compared to facilities with violations was merely 8.9% in 2015.[44] Below are a few examples of enforcement deficiencies:

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[40] Letter from Jon M. Capacasa, Director, EPA Region III Water Protection Division, to Lisa D. Daniels Director, Pa. Dep't of Envtl. Prot. Bureau of Safe Drinking Water (Dec. 30, 2016), https://drive.google.com/file/d/0B4Y3VQLxjkxObjZ0ZXlSVDZvRWc/view.

[41] NATIONAL SUMMARY OF STATE INFORMATION, https://ofmpub.epa.gov/waters10/attains_nation_cy.control (last visited Jul. 31, 2018).

[42] *Id.*

[43] U.S. EPA, Office of Enforcement and Compliance Assurance, *Annual Noncompliance Report (ANCR) Calendar Year 2015* (Aug. 2016), https://echo.epa.gov/system/files/2015_ANCR.pdf.

[44] *Id.* at 7.

- **Tennessee**: The Tennessee Department of Environment and Conservation neglected to timely penalize permit holders despite months of noncompliance, failed to assess appropriate fines, and did not report significant discharge violations from major facilities.[45]
- **Alaska**: EPA regional directors told OIG that "when the region authorized the state to run the program, both the region and OECA officials were aware that the state lacked the capacity to be successful."[46] EPA's State Review Framework for Alaska revealed that, among other serious concerns, the state does not consistently take timely or appropriate enforcement actions, inspect permitted facilities anywhere close to state goals.[47]
- **Louisiana**: Louisiana reviewed the compliance status for less than 50% of individually-permitted non-major NPDES permittees from 2010-2015.[48]

Clean Air Act: State performance also varies widely under the CAA. In 2011, the Office of the Inspector General examined the percentage of facilities inspected, the percentage of significant noncompliance or high priority violations identified per inspection, and the percentage of final actions with penalties for fiscal years 2003-2009 and found that performance varied significantly across the country, in this case "by almost 50 percentage points."[49] Below are a few specific examples of insufficient state enforcement of the CAA:

- **Florida**: The Florida Department of Environmental Protection opened only 18 air enforcement cases in 2015, compared to a previous annual average of 93.[50] Additionally, from 2013 to 2015 the state only filed one asbestos case, compared to a past annual average of 13.[51]
- **North Carolina**: "CAA metric for assessed penalties dropped by 93% statewide from about $235.000 in FY II to just under $17,000 in FY 14. During the same period the number of facilities with informal and formal enforcement actions also dropped dramatically (52% and 79%, respectively)."[52]

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[45] U.S. EPA Region 4, *State Review Framework Tennessee* at 28-35 (Sept. 2016), http://www.documentcloud.org/documents/3173730-TN-Final-SRF-Report-9-29-16.html.
[46] U.S. EPA, Office of Inspector, *EPA Must Improve Oversight of State Enforcement* at 16 (Dec. 2011), https://www.epa.gov/office-inspector-general/report-epa-must-improve-oversight-state-enforcement.
[47] U.S. EPA Region 10, *State Review Framework Alaska* at exec. summary (Dec. 2014), https://www.epa.gov/sites/production/files/2015-01/documents/srf-rd3-rev-ak.pdf.
[48] U.S. EPA, Office of Enforcement and Compliance Assurance, *Annual Noncompliance Report (ANCR) Calendar Year 2015* at 8 (Aug. 2016), https://echo.epa.gov/system/files/2015_ANCR.pdf.
[49] U.S. EPA, Office of Inspector, *EPA Must Improve Oversight of State Enforcement* at 10 (Dec. 2011), https://www.epa.gov/office-inspector-general/report-epa-must-improve-oversight-state-enforcement.
[50] Public Employees for Environmental Responsibility, *Report on Enforcement Efforts by the Florida Department of Environmental Protection* at 23 (Aug. 2016), https://www.peer.org/assets/docs/fl/8_18_16_DEP_Report_on_2015_Enforcement.pdf.
[51] *Id.*
[52] Letter from J. Scott Gordon, Director, EPA Region IV Office of Enforcement Coordination, to Donald R. van der Vaart, Secretary, N.C. Dep't of Envtl. Quality (May 9, 2016), https://assets.documentcloud.org/documents/3114598/EPA-Region-4-Letter-to-NCDEQ.pdf.

- **Ohio**: The Region found that a number of High Priority Violations (HPV) are being resolved by the state through a permit modification/revision. EPA believes that HPV cases should be resolved through a formal enforcement action per the HPV policy, and the state disagrees.[53]

Resource Conservation and Recovery Act: As with the other statutes upon which EPA relies to avoid analyzing exposure pathways, there are serious state enforcement problems with RCRA. For example, Mississippi has not accurately identified and documented RCRA violations.[54] Additionally, despite EPA guidance that states civil penalties should recoup at least the economic benefit the violator gained through noncompliance, the state does not routinely document or consider the economic benefit.[55]

ii) Reduced EPA enforcement provides even less assurance that exposures through the excluded pathways are being effectively managed.

Under the current Administration, enforcement of these environmental statutes has been significantly curbed. For instance, management at EPA has directed EPA investigators to seek authorization before asking companies to conduct testing or sampling under the CAA, RCRA, or the CWA.[56] The memo also states that investigators need authorization if they do not have information specific to a company that it may have violated the law, or if state authorities objected to the tests.[57]

Additionally, in its proposed 2018 budget, the current Administration sought a 31 percent reduction in funding for EPA.[58] This included a 24 percent drop in EPA's enforcement budget, supposedly to avoid "duplication of enforcement actions carried out by the States."[59] The Administration's proposed budget would also cut 45 percent of the EPA grants that states rely on to fund their own enforcement programs.[60]

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[53] U.S. EPA Region 5, *State Review Framework Ohio* at 3, 38-39 (Aug. 2013), https://www.epa.gov/sites/production/files/2014-05/documents/srf-rd2-rev-oh.pdf.
[54] U.S. EPA Region 4, *State Review of Framework Mississippi* at Executive Summary (Mar. 3, 2016), https://www.epa.gov/sites/production/files/2016-03/documents/srf-rd3-rev-ms.pdf.
[55] *Id.* at 24.
[56] Memorandum from Susan Shinkman, Director, EPA Office of Civil Enforcement, to Regional Counsel, Regional Enforcement Directors and Coordinators, and OCE Division Directors (May 31, 2017), https://www.documentcloud.org/documents/4324892-EPA-Clean-Air-Act-and-Its-Power-to-Request.html#document/p60/a392202.
[57] *Id.*
[58] Office of Mgmt. & Budget, *A New Foundation for Greatness, Budget of the U.S. Government, Fiscal Year 2018* at 42 (2017), https://www.whitehouse.gov/sites/whitehouse.gov/files/omb/budget/fy2018/budget.pdf.
[59] Office of Mgmt. & Budget, *Major Savings and Reforms, Budget of the U.S. Government, Fiscal Year 2018* at 86 (2017), https://www.whitehouse.gov/sites/whitehouse.gov/files/omb/budget/fy2018/msar.pdf.
[60] *Id.* at 84.

EPA cannot rely on its actions under other authorities when EPA has itself taken steps to ensure that those authorities are not adequately addressing the risks presented.

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In sum, EPA must analyze all exposures to these chemicals. EPA cannot legally ignore exposures that occur under other EPA-administered statutes, and treating exposures that are known to occur in the world as nonexistent is arbitrary and capricious. EPA must assess these exposures based on their real-world existence and consider how they may combine with other sources of exposure to accurately estimate the risks presented by these chemical substances. Where EPA has inadequate information, EPA should use its information authorities to obtain more information about these exposures.

6. EPA must analyze real-world exposures and not assume perfect compliance with existing regulatory limits.

In a number of the problem formulations, EPA states that in assessing environmental releases, EPA will "consider regulatory limits that may inform estimation of environmental releases."[61] *See, e.g.*, Problem Formulation for Perchloroethylene at p. 66; Problem Formulation for DCM at p. 60. Similarly, EPA suggests that, in assessing occupational exposure, EPA may assume compliance with standards and regulations established by the Occupational Safety and Health Administration (OSHA). *See, e.g.*, Problem Formulation for DCM at p. 63 ("This or other models, including the assumption of compliance with the OSHA [Permissible Exposure Limit] for methylene chloride, may be explored where models specific to conditions of use are not found."); Problem Formulation for Perchloroethylene at p. 69. As established above in Sections 5.I and 6, in reality compliance with regulatory limits is often imperfect, and EPA cannot reasonably assume that all persons are meeting regulatory limits.

For example, the perchloroethylene problem formulation acknowledges that 36 states reported drinking water systems with detections above the regulatory limit. *See, e.g.*, Problem Formulation for Perchloroethylene at p. 41. If EPA assumed compliance with the regulatory limit, EPA would be arbitrary and capricious by relying on a known falsehood.

As another example, "[a] review of five years of state records by the Environmental Integrity Project and Environment Texas shows that the state imposed penalties on *less than 3 percent* of the illegal pollution releases (588 out of 24,839) *reported by* companies during maintenance or malfunctions from 2011 through 2016, even though the incidents released more than 500 million pounds of air pollution."[62] Thus, 500 million pounds of illegal emissions were reported in Texas for 2011 through 2016: it would be irrational to assume that these emissions did not occur. Moreover, the state of Texas did not impose

[61] Given how many environmental releases EPA has excluded outright, it is not always clear what environmental releases EPA will be analyzing.

[62] Environmental Integrity Project, *Breakdowns in Enforcement Texas Rarely Penalizes Industry for Illegal air Pollution Released during Malfunction and Maintenance* at 1 (Jul. 2017), https://www.environmentalintegrity.org/wp-content/uploads/2017/02/Breakdowns-in-Enforcement-Report.pdf (emphases added).

penalties for 97% of these illegal pollution releases reported by companies. Of course, not all violations are promptly or accurately reported by companies, so this number may actually overestimate the level of compliance and enforcement. With such lax enforcement, compliance levels are going to be low.

Given known limitations in enforcement and compliance, it would be arbitrary and capricious for EPA to assume perfect compliance with existing regulatory limits. Instead, EPA should rely on real-world, reasonably available information.

7. EPA needs to analyze potential exposures from distribution, as well as from known and reasonably foreseeable accidental exposures.

The problem formulations generally acknowledge the need to analyze activities related to a chemical's distribution, but EPA will need to analyze these exposures more robustly than the problem formulations currently reflect. *See, e.g.*, Problem Formulation for Perchloroethylene at p. 33.

The problem formulations give no attention to potential releases and exposures resulting from accidental releases. EDF does not suggest that EPA needs to consider every possible scenario, but the risk of accidental releases and exposures is very real and certainly "reasonably foreseen" in many respects, and EPA has authority to mandate steps to reduce those risks. For example, as and after Hurricane Harvey passed through Houston, over 40 sites released toxic chemicals into the environment.[63] Given the known accidental releases, the huge number of petrochemical plants and refineries in the Houston area, and the likelihood that flooding there may become more common in light of climate change, such events are clearly reasonably foreseen and hence EPA needs to give more consideration to the potential for accidental releases.

8. EPA must consider "reasonably available" information, and thus EPA must use its authorities under TSCA §§ 4 and 8 to obtain additional information.

TSCA orders EPA to consider "available" and "reasonably available" information in crafting a risk evaluation, 15 U.S.C. §§ 2605(b)(4)(F)(i), 2625(k), and under the new risk evaluation rule, EPA defined "[r]easonably available information" to mean "information that EPA possesses or can reasonably generate, obtain, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation." 40 C.F.R. § 702.33, promulgated at 82 Fed. Reg. 33,748 (July 20, 2017). Thus, under its own rule, EPA has to consider information that it "can reasonably generate, obtain, and synthesize."

In our prior comments on the scope documents, EDF expanded on EPA's duties to use its authorities under TSCA §§ 4 and 8 to obtain additional information about these ten chemicals, and EDF incorporates those arguments here.[64] In response to EDF's comment, EPA acknowledged its duty to consider

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[63] *See, e.g.*, *More Than 40 Sites Released Hazardous Pollutants Because of Hurricane Harvey*, N.Y. TIMES (Sept. 8, 2017), https://www.nytimes.com/interactive/2017/09/08/us/houston-hurricane-harvey-harzardous-chemicals.html?_r=0.

[64] EDF Comments on Ten Scopes under the Toxic Substances Control Act at pp. 11-16, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069.

"reasonably available information" and EPA described its efforts to gather information up to this point.[65] While EPA details its "data gathering activities," EPA has not established that these activities will result in EPA obtaining all the reasonably available information that EPA could "generate, obtain, and synthesize" if EPA also used its authorities under TSCA §§ 4 and 8 to obtain additional information. Thus, EPA has not established that it will obtain all reasonably available information.

In particular, EDF's prior comments established that relying solely on voluntary requests for information, may result in limited, biased, inaccurate, or incomplete information on the chemicals. EDF incorporates those arguments here.[66] EPA's response to this comment was that "EPA has not indicated it would rely solely on voluntary requests for information."[67] Thus, EPA appears to recognize that voluntary requests standing alone are insufficient. Despite that acknowledgement, EPA still has not relied on its available authorities to obtain additional information. EDF urges EPA to do so.

EPA's primary response to EDF's request that EPA consider all reasonably available information appears to be that the information EPA currently has is "adequate."[68] But, as a general matter, EPA has to consider all reasonably available information; TSCA does not authorize EPA to stop its analysis on the basis that EPA believes its current information is adequate. And as explained more below, it is clear that the information is not yet adequate to meet EPA's obligations under TSCA.

A. Relying on voluntary requests for information will result in limited, biased, inaccurate, or incomplete information on the chemicals.

In all but one of the problem formulations, EPA includes this or very similar language: *"EPA encourages submission of additional existing data, such as full study reports or workplace monitoring from industry sources*, that may be relevant for refining conditions of use, exposures, hazards and potentially exposed or susceptible subpopulations during the risk evaluation. EPA will continue to consider new information submitted by the public." Problem Formulation for 1-BP at p. 57 (emphasis added); *see also* Problem Formulation for Asbestos at p. 47; Problem Formulation for 1,4-Dioxane at p. 47; Problem Formulation for Carbon Tetrachloride at p. 53; Problem Formulation for HBCD at p. 56; Problem Formulation for DCM at p. 59; Problem Formulation for NMP at p. 53; Problem Formulation for Perchloroethylene at p. 65; Problem Formulation for TCE at p. 58.

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[65] EPA's Responses to Public Comments Received on the Scope Documents for the First Ten Chemicals for Risk Evaluation under TSCA at pp.10-14, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0725-0051.

[66] EDF Comments on Ten Scopes under the Toxic Substances Control Act at pp. 16-20, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069.

[67] EPA's Responses to Public Comments Received on the Scope Documents for the First Ten Chemicals for Risk Evaluation under TSCA at p.13, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0725-0051.

[68] *See id.* at pp. 13, 10-14.

With this language EPA seems to acknowledge the serious data gaps it faces; yet despite clear authority to require workplace monitoring by industry and to obtain full study reports using its existing authorities, EPA resorts merely to encouraging their submission.

Rather than relying solely on voluntary submissions—an approach that has proven insufficient in the past—EPA should use its information authorities to obtain necessary information on conditions of use, exposures, hazards, and potentially exposed or susceptible subpopulations.

There are several obvious problems and limitations with this voluntary approach which EPA has still not addressed.

First, a voluntary call is much less likely to produce all of the necessary information than rules mandating that affected parties provide the requested information. If manufacturers and processors are legally required to provide the information, that legal obligation provides a strong incentive for them to develop or obtain and submit all relevant information. Absent that incentive, some companies may choose to focus time and attention on other matters.

Second, EPA has provided no empirical evidence establishing that this voluntary approach will result in EPA obtaining all "reasonably available" information. Unless EPA has some empirical basis for stating that the voluntary approach will allow EPA to obtain all reasonably available information that it can obtain under its legal authorities, EPA must rely on its existing authorities to obtain a complete set of information.

Third, manufacturers and processors of these chemicals have a vested interest in EPA finding that the chemicals do not present an unreasonable risk. A no-unreasonable-risk finding reduces the likelihood of government regulation, including potential restrictions on risky chemicals, and it may reduce any stigma they may otherwise face in the marketplace. The financial costs of regulation may ultimately be very high for some specific firms and individuals, and even if not, many firms and individuals may believe that the costs of regulation will be high. These companies have a "financial interest" in the outcome of these proceedings, and they are not impartial. *See, e.g.*, 28 U.S.C. § 455(b)(4) (requiring Judges to disqualify themselves in proceedings where they have a financial interest). Because of this reality and appearance of partiality, relying solely on voluntary measures decreases the credibility of these risk evaluations.

Relying solely on voluntary presentation of information raises the concern that the companies or trade associations may present an incomplete or skewed picture. Companies and trade associations may choose to "cherry pick" information and provide only the information that paints their chemicals in favorable light. They may provide only summaries of information that reflect conscious and subconscious judgment calls that result in unduly favorable conclusions; and without access to the full information neither EPA nor the public can independently assess such conclusions. They may choose not to review records robustly when the review may disclose unfavorable information. They may seek to put their best foot forward and describe the ideal scenario of use and safety measures. Or, if they have unfavorable information, they may choose not to provide any information at all and simply not participate in these proceedings.

EPA cannot simply assume that members of the regulated community will voluntarily disclose unfavorable or complete information about their practices and products. *See* THE FEDERALIST NO. 51 (James Madison) ("If men were angels, no government would be necessary. *** [E]xperience has taught mankind the necessity of auxiliary precautions."); *Williams v. Pennsylvania*, 136 S. Ct. 1899, 1905-06 (2016) ("Bias is easy to attribute to others and difficult to discern in oneself. *** This objective risk of bias is reflected in the due process maxim that 'no man can be a judge in his own case and no man is permitted to try cases where he has an interest in the outcome.'"). Here, manufacturers and processors obviously have an interest in the outcome, and EPA must craft its procedures and approaches with that reality in mind. Requiring the submission of information is the safest approach to ensuring that these parties provide all relevant information, and that is in turn crucial to establishing and demonstrating the credibility of this process.

If EPA acts under TSCA §§ 8(a), (c), and (d), the regulations impose some requirements that will help ensure the accuracy and completeness of the information. First, EPA can require that certain information and underlying information be provided in full, which ensures completeness. In addition, a § 8(d) rule requires that people engage in an adequate search of records. 40 C.F.R. § 716.25. Second, submitters must file certification statements by authorized officials that certify that the submitted information has been submitted in compliance with the requirements of this process. *See, e.g.*, 40 C.F.R. § 711.15(b)(1). Third, submitters often must retain records of required submissions for a period of five years, and the retention of records can help encourage accurate reporting since those records would be available should a submission latter be investigated. *See, e.g.*, 40 C.F.R. § 711.25. None of these features apply to the voluntary requests for information EPA has indicated it is relying on.

B. EPA cannot rationally rely on unvetted industry submissions, and to the extent EPA relies on voluntary submissions from industry, EPA must take numerous additional steps to increase their reliability and transparency.

In the problem formulations, EPA uncritically relies on industry submissions, and this reliance does not constitute the best available science. In the most extreme examples, EPA cites to a piece of correspondence where the actual text of the correspondence is not available, nor are the surrounding circumstances or any supporting evidence. *See, e.g.*, Problem Formulation for HBCD at p. 31. From these records, it is not possible for the public to even begin to assess the accuracy of the underlying statements or EPA's conclusions based on them.

In many problem formulations, EPA cites and uses data obtained from the European Chemicals Agency (ECHA). *See, e.g.*, Problem Formulation for 1-BP at pp. 41-42; Problem Formulation for 1,4-Dioxane at pp. 33-35; Problem Formulation for Carbon Tetrachloride at pp. 31-32, 39; Problem Formulation for HBCD at pp. 21, 36, 51; Problem Formulation for NMP at pp. 32, 39; Problem Formulation for PV 29 at pp. 7-8, 12-14, 21-22, 26-28, 31-32, 37; Problem Formulation for TCE at p. 39.

However, in most cases the data are simply those submitted by companies to ECHA in the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registration dossiers, and the data have not been independently evaluated by ECHA or other government authorities in the EU. In citing

information available through ECHA, EPA must clearly distinguish between industry data that have not been evaluated, industry data that have been evaluated by ECHA or other government authorities in the EU, and information that ECHA has itself developed or provided.

To the extent it relies on voluntary submissions from industry, EPA needs to take additional steps to better ensure that the voluntary information it receives is accurate and complete. EPA would need to develop a far more rigorous and structured process than it currently has. For example, EPA's submission process does not appear to require anyone to certify that the information in their submissions is accurate or complete to the best of their knowledge. EPA should consider approaches for vetting statements and assertions, particularly when made by entities with a financial interest in the outcome of these risk evaluations.

C. EPA must obtain and make public the full studies.

EPA needs to ensure it has obtained copies of the full studies for which it cites ECHA as the source. EPA should also request that submitters always provide copies of full studies, as well as underlying data whenever reasonably available or obtainable. Setting aside concerns about partiality, EPA needs the underlying data to ascertain the accuracy of the information and associated statements or conclusions, as well as to determine how much confidence or uncertainty applies to a particular submission.

EPA also needs to make copies of full studies on which it relies available to the public, including those to which it refers in the problem formulations as identified in the European Chemicals Agency (ECHA) Database and FDA's Food Additive Petitions. *See, e.g.*, Problem Formulation for PV 29 at p. 7. As EDF has explained in prior comments, there are numerous reasons that it is important that the public have access to full studies and the underlying information, not simply robust or other study summaries.[69] Without access to full studies, the public will be challenged or unable to assess and comment on the quality of the studies used by the agency, including the extent to which the requirements of section 26(h) and 26(i) are met. Even the best study summaries are incomplete descriptions that do not allow for an independent examination of study quality and conclusions reached by authors. Common examples of such conclusions include, "findings were not statistically significant," "findings are within the range of historical controls," and "effects observed were non-linear [and therefore biologically questionable or irrelevant]." Divorced from the details of the actual design and results of a study, it is impossible to evaluate the appropriateness of such conclusions. It is important that EPA obtain the full studies, both so that EPA staff have access and so that EPA can make them publicly available. EPA should make such information public and easily searchable through online portals such as the Health and Environmental Research Online (HERO) database. EDF incorporates and reiterates the numerous points made in support of public access to the full studies here. *Id.* These points also support the importance of EPA obtaining the full studies.

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[69] *See, e.g.*, EDF Comments on Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act at p.37, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0654-0074.

D. Both the problem formulations and these comments identify numerous information gaps that EPA needs to fill using its information authorities.

Throughout these comments, EDF points to information gaps that EPA should fill with its information authorities. For example, EPA states that the available information on perchloroethylene is "insufficient to allow for a quantitative assessment of the impact of susceptibility on risk," and EPA appears to exclude certain susceptible subpopulations from analysis on this basis. Problem Formulation for Perchloroethylene at p. 53. But the available information identifies numerous subpopulations as possibly more susceptible to adverse effects. In these circumstances, EPA should use its information authorities to obtain additional information about susceptibility so that EPA can fulfill its duty to consider unreasonable risks to potentially exposed or susceptible subpopulations. Similarly, EPA should use its information authorities to fill the other gaps identified in these comments as well.

9. EPA needs to implement the requirements of TSCA § 14 when reviewing materials for the risk evaluations.

EPA has an affirmative obligation to review at least 25% of non-chemical identity confidentiality claims under TSCA, 15 U.S.C. § 2613(g), and EPA has stated that it is implementing that obligation by "review[ing] every fourth submission received that contains non-chemical identity [confidential business information (CBI)] claims."[70] Thus, on balance, EPA should be reviewing all confidentiality claims asserted in at least approximately one-fourth of the information submissions it receives. Those claims must be substantiated at the time of submission. EPA must complete reviews of confidentiality claims within 90 days of receipt of the claims, and if EPA denies a claim, EPA must disclose the information that had been claimed confidential 30 days after notifying the claimant of the denial, absent a challenge to the denial in district court. 15 U.S.C. § 2613(g)(1)(A), (g)(2)(B).

In addition, TSCA requires disclosure of "any health and safety study which is submitted under [TSCA] with respect to *** any chemical substance or mixture *** for which notification is required under section 5." 15 U.S.C. § 2613(b)(2)(A). TSCA also requires disclosure of "any information reported to, or *otherwise obtained by*, [EPA] *from* a health and safety study which relates to [such] a chemical substance. . . ." *Id*. § 2613(b)(2)(B) (emphases added). Thus, any health and safety studies and related information on these chemicals must be disclosed. TSCA defines "health and safety study" to mean "any study of any effect of a chemical substance or mixture on health or the environment or on both, including underlying information and epidemiological studies, studies of occupational exposure to a chemical substance or mixture, toxicological, clinical, and ecological studies of a chemical substance or mixture, and any test performed pursuant to this Act." *Id*. § 2602(8). EPA has provided further details on this expansive definition of "health and safety study," explaining that it encompasses, among other things, "[a]ny data that bear on the effects of a chemical substance on health or the environment" and "[a]ny assessments of risk to health and the environment resulting from the manufacture, processing, distribution in commerce, use, or disposal of the chemical substance." 40 C.F.R. § 720.3(k). Thus, any

[70] EPA REVIEW AND DETERMINATION OF CBI CLAIMS UNDER TSCA, https://www.epa.gov/tsca-cbi/epa-review-and-determination-cbi-claims-under-tsca (last visited Jan. 18, 2018).

health and safety study or other information on health or environmental effects or any assessment of risk EPA prepared must be disclosed. The only exception from that disclosure requirement is for "information *** that discloses processes used in the manufacturing or processing of a chemical substance or mixture or, in the case of a mixture, the portion of the mixture comprised by any of the chemical substances in the mixture." 15 U.S.C. § 2613(b)(2).

In developing these risk evaluations, a large fraction of the information EPA relies on will constitute health and safety studies. All such information not subject to the two narrow exceptions needs to be made public.

10. EPA should generally utilize its prior hazard and/or dose-response values for 1,4-dioxane, carbon tetrachloride, methylene chloride, perchloroethylene, and trichloroethylene, and EPA must explain any decision to deviate from these values.

In the last decade, EPA's Integrated Risk Information System has developed hazard and/or dose-response values for 1,4-dioxane, carbon tetrachloride, methylene chloride, perchloroethylene, and trichloroethylene. EPA should not lightly disregard this valuable work, and EPA has shown a willingness to rely on these values in the past. For each chemical, EPA must identify and explain any decision to deviate from these values, as well as the scientific basis for such deviation.

For example, in the problem formulation for trichloroethylene, EPA states:

> TCE has an existing EPA IRIS Assessment (U.S. EPA, 2011c) and an ATSDR Toxicological Profile (ATSDR, 2014a); hence, many of the hazards of TCE have been previously compiled and systematically reviewed. Furthermore, EPA previously reviewed data/information on health effects endpoints, identified hazards and conducted dose-response analysis in the TSCA Work Plan Chemical Risk Assessment of TCE (U.S. EPA, 2014c). EPA has relied heavily on these comprehensive reviews in preparing this problem formulation. EPA expects to use these previous analyses *as a starting point for identifying key and supporting studies* to inform the human health hazard assessment, including dose-response analysis. The relevant studies will be evaluated using the data quality criteria in the Application of Systematic Review in TSCA Risk Evaluations document (U.S. EPA, 2018).

Problem Formulation for TCE at p. 44 (emphasis added).

The agency indicates that "many of the hazards of TCE have been previously compiled and systematically reviewed," which was in fact done in the ATSDR profile and the IRIS toxicological review. As noted in EPA's Work Plan assessment, EPA relied heavily on the IRIS toxicological review to develop the Work Plan assessment. In describing the IRIS toxicological review, EPA stated in the Work Plan Assessment:

> The assessment uses the hazard and dose-response information published in the final toxicological review that the U.S. EPA's Integrated Risk Information System (IRIS)

> published in 2011 (EPA, 2011e). The TCE IRIS assessment used a weight-of-evidence approach, the latest scientific information and physiologically-based pharmacokinetic (PBPK) modeling to develop hazard and dose-response assessments for TCE's carcinogenic and non-carcinogenic health effects resulting from lifetime inhalation and oral exposures. In addition to relying on the latest scientific information, the TCE IRIS assessment underwent several levels of peer review including agency review, science consultation on the draft assessment with other federal agencies and the Executive Office of the President, public comment, external peer review by the EPA's Science Advisory Board (SAB) in 2002, scientific consultation by the U.S. National Academy of Sciences (NAS) in 2006, external peer review of the revised draft assessment by the EPA's Science Advisory Board (SAB) in January 2011, followed by final internal agency review and EPA-led science discussion on the final draft.[71]

Given EPA's multiple, clear statements affirming the scientific rigor of the IRIS toxicological review as well as its decision to rely upon it in its 2014 Work Plan Assessment (Congress itself has given the Work Plan significant weight under TSCA), EPA must identify and explain any decision to deviate from these reviews and clearly identify in its draft risk evaluation any modifications it proposes in hazard identification and dose-response characterization, and the scientific basis for them. Any such differences must be based on compelling scientific evidence and explicitly interrogated through the peer review process.

The excerpt from the problem formulation refers to "key," "supporting," and "relevant" studies. The meaning of these descriptors is entirely unclear. EPA must explicitly define the meaning of these terms and their implications with regard to the agency's approach to systematic review and risk evaluation.

11. EPA needs to accurately identify the relevant potentially exposed or susceptible subpopulations.

A. EPA needs to identify infants, children, pregnant women, and adults of childbearing age as potentially exposed or susceptible subpopulations as appropriate for 1-BP, carbon tetrachloride, HBCD, methylene chloride, N-methylpyrrolidone, perchloroethylene, and trichloroethylene.

TSCA requires that EPA identify "the potentially exposed or susceptible subpopulations the Administrator expects to consider" in the scopes. 15 US.C. § 2605(b)(4)(D). EPA largely failed to identify these populations in the scopes, and EPA still has failed to identify many of them in the problem formulations. While EPA has, to some extent, considered some of those at greater risk due to increased exposure in the problem formulations, the agency too often defers the process of identifying populations with greater susceptibility to the risk evaluation stage.

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[71] U.S. EPA, *TSCA Work Plan Chemical Risk Assessment Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses* at 20-21 (June 2014), https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf.

TSCA § 3(12) states that "the term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population identified by the Administrator who, due to *** greater susceptibility *** may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly." 15 U.S.C. § 2602(12). Where the evidence before the agency shows that a chemical presents developmental or reproductive risks, then the evidence establishes that infants, children, pregnant women, and adults of child-bearing age "may be at greater risk than the general population of adverse health effects," and EPA must identify them as potentially exposed or susceptible subpopulations.

Based on the evidence already before the agency, EPA must identify these groups as potentially exposed or susceptible subpopulations for 1-BP, carbon tetrachloride, HBCD, DCM, NMP, perchloroethylene, and trichloroethylene. Problem Formulation for 1-BP at p. 44 (describing evidence of reproductive and developmental toxicity for 1-BP); Problem Formulation for Carbon Tetrachloride at p. 74 (recognizing need to rescreen for reproductive and developmental toxicity); Problem Formulation for HBCD at p. 43 (describing evidence of reproductive and developmental hazards); Problem Formulation for NMP at pp. 40-41 (recognizing that a "continuum of biologically relevant reproductive/developmental effects have been reported following NMP exposure" and noting that EPA previously identified young children and pregnant women as potentially susceptible); Problem Formulation for Perchloroethylene at p. 52 (discussing numerous studies suggesting both reproductive and developmental toxicity); Problem Formulation for TCE at p. 45 (identifying TCE as a developmental toxicant). In addition, there are data on developmental neurotoxicity for DCM that EPA failed to mention in the problem formulation.[72]

B. EPA should identify people living near disposal sites as potentially exposed or susceptible subpopulations.

EPA should identify people living near disposal sites as potentially exposed or susceptible subpopulations. These groups include (but are not limited to) those living near so-called "legacy" disposal sites. To be clear, many disposal sites are associated with activities that reflect ongoing or prospective manufacturing, processing, distribution, or use, so EPA must analyze those disposals and disposal sites even assuming EPA were correct about its asserted authority to ignore so-called legacy uses, associated disposal, and legacy disposal. But EPA should analyze all disposal sites and populations living in proximity to them; the distinctions EPA has drawn between disposals find no basis in the statute, and as explained below, TSCA expressly requires EPA to consider disposal.

As EDF previously explained in its comments on the scopes, EPA cannot rationally exclude so-called legacy uses and associated disposals. EDF incorporates and reiterates those points here as well.[73] For the same reasons, EPA cannot rationally exclude so-called legacy disposals. Along with other

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[72] *See* U.S. EPA, *TSCA Work Plan Chemical Risk Assessment Methylene Chloride: Paint Stripping Use* at 80-81 (Aug. 2014), https://www.epa.gov/sites/production/files/2015-09/documents/dcm_opptworkplanra_final.pdf.

[73] EDF Comments on Ten Scopes under the Toxic Substances Control Act pp.8-9, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069.

petitioners, EDF has further developed these arguments in a Brief which is attached as Appendix A. EDF incorporates and reiterates those points here. *See* Appendix A at 40-51.

In sum, a chemical's conditions of use include "the circumstances" under which the chemical is "known, or reasonably foreseen to be manufactured, processed, distributed in commerce, *used, or disposed of*." 15 U.S.C. § 2602(4) (emphasis added). Because the definition uses a disjunctive "or" list, each lifecycle stage of a chemical, standing alone, is a condition of use, even if some of the chemical's lifecycle stages have been discontinued. *See, e.g.*, *Horne v. Flores*, 557 U.S. 433, 454 (2009). So-called legacy disposals are "circumstances" under which a chemical is "known *** to be *** disposed of." 15 U.S.C. § 2602(4). As the Senate Report accompanying an early version of the amended TSCA acknowledged, "there may be exposures of concern from substances that are not currently or no longer in commerce, and the section provides EPA authority to prioritize inactive substances that meet certain criteria." S. Rep. No. 114-67, at 11. "Disposal" of a chemical substance (including products containing that substance) is not a one-time occurrence when the substance or product is buried or placed in a landfill or other waste facility, but remains ongoing after the initial act of discard. Moreover, even in its flawed risk evaluation rule, EPA stated that "EPA may consider background exposures from legacy use, associated disposal, and legacy disposal as part of an assessment of aggregate exposure or as a tool to evaluate the risk of exposures resulting from non-legacy uses." 82 Fed. Reg. at 33,730. Thus, even if EPA follows its illegal rule (which it should not—EPA should give full weight to the consideration of the exposures arising from these conditions of use), EPA should consider these exposures in assessing the combined exposure faced by subpopulations near disposal sites.

Thus, EPA must analyze the exposures arising from the activities associated with disposal of a chemical substance. EPA must also identify those who face greater exposures due to their proximity to disposal sites as a "potentially exposed or susceptible subpopulation" since they are a "group of individuals within the general population identified by the Administrator who, due to *** greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture." 15 U.S.C. § 2602(12). EPA correctly recognizes that those "who live or work near manufacturing, processing, distribution or use sites" qualify as potentially exposed or susceptible subpopulations, *see, e.g.*, Problem Formulation for Perchloroethylene at p. 47. Thus, EPA recognizes that proximity to other conditions of use lead to greater exposure, but in many of the problem formulations, *see, e.g.*, *id*., EPA irrationally ignores the potential for greater exposure to arise from proximity to disposal activities. As a matter of law, EPA must analyze this susceptible subpopulation as well. EPA should consider those who live near disposal locations, regardless of whether that disposal is so-called "legacy disposal" or "associated disposal."

Notably, in some problem formulations, EPA correctly acknowledges that it must analyze these vulnerable subpopulations. *See, e.g.*, Problem Formulation for 1,4-Dioxane at p. 32 ("Other groups of individuals within the general population who may experience greater exposures due to their proximity to conditions of use identified in Section 2.2 that result in releases to the environment and subsequent exposures (e.g., individuals who live or work near manufacturing, processing, distribution, use or *disposal sites*).") (emphasis added). EPA's correct conclusion that these subpopulations merit additional analysis for some chemicals highlights that it is irrational to exclude these subpopulations for others.

Problematically, even when EPA recognizes that it must analyze those facing greater exposure due to proximity to disposal, EPA often excludes the pathways leading to this exposure from further analysis. *E.g., compare* Problem Formulation for 1,4-Dioxane at p. 32 (recognizing subpopulation), *with id*. at 44-45 (excluding disposal pathway from analysis). As EDF previously explained, this approach is irrational and incoherent. *See* above in Section 5.B.ii. EPA should not exclude those pathways for the reasons given above, and in addition, EPA cannot rationally evaluate the greater exposure these subpopulations face without analyzing these pathways. EPA has provided no rationale explaining how it plans to accurately evaluate the risks faced by these subpopulations while ignoring these pathways of exposure.

In addition, EPA should be analyzing communities who live or work near past manufacturing, processing, distribution, or use sites, even if those activities have ceased. The statute does not allow EPA to ignore conditions of use merely because they happened in the past, and in any event, the disposal at these sites remains ongoing at this time.

C. EPA should identify people living in proximity to sources of contamination as potentially exposed or susceptible subpopulations.

Most of the problem formulations correctly identify people subject to greater exposure due to their proximity to conditions of use as a potentially exposed or susceptible subpopulation.[74] For example, the 1-BP problem formulation acknowledges the need to identify this subpopulation:

> EPA identifies the following as potentially exposed or susceptible subpopulations that EPA expects to consider in the risk evaluation due to their greater exposure:
>
> ***
>
> - Other groups of individuals within the general population who may experience greater exposures due to their proximity to conditions of use identified in Section 2.2 that result in releases to the environment and subsequent exposures (e.g., individuals who live or work near manufacturing, processing, use or disposal sites).

Problem Formulation for 1-BP at p. 40; Problem Formulation for Asbestos at p. 32; Problem Formulation for 1,4-Dioxane at p. 32; Problem Formulation for HBCD at p. 39; Problem Formulation for DCM at p. 40; Problem Formulation for NMP at p. 37; Problem Formulation for Perchloroethylene at p. 47; Problem Formulation for TCE at p. 38.

However, such subpopulations may extend further to those in proximity to sources of contamination not necessarily linked to or able to be attributed to a specific condition of use. For example, for many of the

[74] EPA fails to identify this subpopulation for two chemicals: carbon tetrachloride and PV 29. EPA should include these subpopulations for those two chemicals as well. The reasoning that supports identifying these subpopulations for the other chemicals similarly applies here, absent a compelling explanation for excluding these subpopulations.

problem formulation chemicals, EPA has identified soil or groundwater contamination that leads to potential elevated exposures of people nearby.

TSCA defines the term "potentially exposed or susceptible subpopulation" to include "a group of individuals within the general population identified by the Administrator who, due to *** *greater exposure*, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture." 15 U.S.C. § 2602(12) (emphasis added). Thus, a subpopulation can qualify due solely to "greater exposure" to a chemical substance; the statute includes no text qualifying "greater exposure" requiring that the exposure be linked to a particular condition of use.

Thus, EPA needs to expand its list to include:

- Other groups of individuals within the general population who may experience greater exposures due to their proximity to sources of contamination (e.g., contaminated groundwater) not necessarily linked to or able to be attributed to a specific condition of use.

D. Reasonably available information reveals numerous sites where these chemicals are known to be present and thus where the subpopulations in their proximity may be at greater risk due to greater exposure.

Reasonably available information reveals that numerous sites exist where these chemicals are known to be present, leading to greater potential exposures for the subpopulations living in proximity to these sites. We summarize some of the available information below. In addition, we attach a list of some of the known sites with these chemical substances so that EPA can analyze the subpopulations potentially suffering greater exposure from these sites. *See* Appendix B.

Chemical Substance	**Number of Final and Proposed Superfund Sites with the Chemical Substance[75]**
1,4-dioxane	37
Asbestos	51
Carbon tetrachloride	240
Methylene chloride	394
Tetrachloroethylene	394
Trichloroethylene[76]	364

[75] These data come from the National Institute of Health's (NIH) ToxMap, available at https://toxmap.nlm.nih.gov/toxmap/app/.

[76] For trichloroethylene ToxMap had an option to select both "trichloroethylene" and "TCE" as Superfund pollutants. The number included in the table comes from the search for "trichloroethylene"

12. EPA needs to ensure that environmental justice is appropriately considered, analyzed, and addressed in the risk evaluations.

Environmental justice is "the fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation and enforcement of environmental laws, regulations and policies."[77] According to EPA, providing "[f]air treatment" will ensure that "no group of people should bear a disproportionate share of the negative environmental consequences resulting from industrial, governmental and commercial operations or policies."[78] EPA has committed to integrate environmental justice into "everything" the agency does in order to "reduce[ ] disparities in the nation's most overburdened communities."[79]

Despite this commitment, and EPA's obligations to comply with Executive Order 12898 (see below), EPA has not incorporated environmental justice considerations into the problem formulations. In addition, EPA does not appear to have undertaken any outreach oriented towards ensuring the meaningful involvement of environmental justice communities in the risk evaluation process. EPA must address environmental justice in the risk evaluations, both by incorporating an analysis into the evaluations and ensuring meaningful involvement by environmental justice communities in the development of the risk evaluations.

A. The risk evaluations are subject to Executive Order 12898.

Executive Order 12898 directed federal agencies to identify and address "disproportionately high and adverse human health or environmental effects of its programs, policies, and activities on minority populations and low-income populations." Exec. Order No. 12898, 59 Fed. Reg. 7629 (Feb. 16, 1994). EPA must comply with this duty in the Executive Order. *See Sherley v. Sebelius*, 689 F.3d 776, 784 (D.C. Cir. 2012) ("[A]s an agency under the direction of the executive branch, it must implement the President's policy directives to the extent permitted by law."). The Executive Order applies, by its own terms, to all "programs, policies, and activities" of a federal agency, and EPA's preparation of the risk evaluations undoubtedly fall within this capacious definition, qualifying as "activities" of EPA, carried out as part of its "programs" and pursuant to its "policies." As agency actions that may affect the level of protection provided to human health or the environment, the risk evaluations under TSCA must address environmental justice communities.[80] EPA's own guidance on considering environmental justice defines

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only. The search for "TCE" results in 264 final and proposed Superfund Sites. Because some of these sites overlap, but not entirely, we kept the higher number in the table.

[77] EJ 2020 GLOSSARY, https://www.epa.gov/environmentaljustice/ej-2020-glossary.

[78] *Id.*

[79] U.S. EPA, *EJ 2020 Action Agenda* at 1 (2016), https://www.epa.gov/sites/production/files/2016-05/documents/052216_ej_2020_strategic_plan_final_0.pdf.

[80] *See* U.S. EPA, *EPA's Action Development Process Interim Guidance on Considering Environmental Justice During the Development of an Action* at 18 (Jul. 2010), https://www.epa.gov/sites/production/files/2015-03/documents/considering-ej-in-rulemaking-guide-07-2010.pdf.

"agency action" to include risk assessments.[81] EPA has articulated no theory for why the Executive Order would not apply to the risk evaluations.

Yet EPA has failed to mention, let alone adequately address, Executive Order 12898 or "environmental justice" in the problem formulations. Failure to do so violates EPA's obligations under the Executive Order.

Notably, EPA has stated that the identification of potentially exposed or susceptible subpopulations under TSCA would "carry[ ] out the spirit" of Executive Order 12898.[82] EPA's implication that the act of merely identifying "potentially exposed or susceptible subpopulations," standing alone, is sufficient to comply with the Executive Order, is plainly incorrect. The Executive Order specifically states that EPA must consider the disparate impacts of pollution on "minority populations and low-income populations."[83] The failure to do so in the problem formulation documents, in particular by failing to consider minority, low-income, and indigenous communities when identifying potentially exposed or susceptible populations, does not "carry out the spirit," or the letter, of the Executive Order. EPA must prepare an actual environmental justice analysis to comply with the Executive Order.

B. EPA's exclusions in the problem formulations violate the Executive Order by underestimating the risks faced by environmental justice communities.

EPA's decision to exclude environmental releases covered by other statutes because those statutes "adequately address" risk fails to acknowledge that other statutes have historically failed to consider environmental justice communities in permitting and enforcement. The National Environmental Justice Advisory Council (NEJAC), a federal advisory committee to EPA, has stated that:

> Environmental protection in this country has grown by individual pieces of legislation, developed to address a particular environmental media or a pressing problem like abandoned toxic sites. Environmental law has not evolved from a master game plan or unifying vision. As a result, the statutes *have gaps in coverage* and do not assure compatible controls of environmental releases to all media from all sources.[84]

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[81] *Id.* at 1.

[82] U.S. EPA, Risk Evaluation Rule Response to Comments at 1, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0654-0109.

[83] Exec. Order No. 12898; *see also* U.S. Office of Inspector General, *EPA Needs to Consistently Implement the Intent of the Executive Order on Environmental Justice* at 9-10 (Mar. 2004), https://www.epa.gov/sites/production/files/2015-10/documents/20040301-2004-p-00007.pdf (explaining that the intent of the Executive Order, in part, was to place EPA's focus on minority and low-income communities).

[84] National Environmental Justice Advisory Council, Cumulative Risks/Impacts Work Group, *Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and cumulative Risks/Impacts* at 7 (Dec. 2004), https://www.epa.gov/sites/production/files/2015-04/documents/ensuringriskreducationnejac.pdf (emphasis added).

Those gaps in coverage were often a result of controlling pollution solely "through technology-based regulation or an individual chemical-by-chemical approach."[85] The Lautenberg Act's unique emphasis on protecting "potentially exposed or susceptible subpopulations" recognized, in part, that the historical regulation of pollutants resulted in some subpopulations, including low-income, minority, and indigenous communities, being disproportionately impacted by chemical contamination.

In addition to the general gaps in coverage, environmental justice communities are often disproportionately exposed to sources of chemical contamination. For instance, a report by the General Accounting Office revealed that:

- three-quarters of hazardous waste landfill sites in eight southeastern states were located in communities whose residents were primarily poor and African-American or Latino, and
- race and ethnicity were the most significant factors in deciding where to place landfills, waste and environmentally hazardous facilities.[86]

EPA's exclusion from the problem formulations of exposure pathways resulting from environmental releases fails to recognize that environmental justice communities have not historically been protected by other environmental statutes and are often disproportionately exposed to chemical substances through disposal and other conditions of use. These exclusions will result in unfair treatment to environmental justice communities by ensuring that they will continue to "bear a disproportionate share of the negative environmental consequences resulting from industrial, governmental and commercial operations or policies."[87]

Moreover, EPA's exclusions of exposure pathways linked to disposal sites and legacy use, associated disposal, and legacy disposal will specifically underestimate the exposures of environmental justice communities. In fact, NEJAC has previously informed EPA of this exact concern:

> It is particularly important to recognize historical exposures in communities and tribes suffering environmental injustice. In some cases, community members were exposed to pollutants for many years in the past from facilities that are *no longer functioning or in business*. These past exposures could act to increase the body burden of a subpopulation so that vulnerable individuals start off at a higher dose. Even if the dose-response curves among the subpopulation are the same as the general population, starting off at a higher point on this curve puts the members of the vulnerable subpopulation at greater risk for exposure to the same amount of a compound than the

[85] *Id.* at 11.
[86] General Accounting Office, *Siting Hazardous Waste Landfills and Their Correlation with Race and Economic Status of Surrounding Communities* at 13-21 (1983), https://www.gao.gov/products/RCED-83-168.
[87] EJ 2020 GLOSSARY, https://www.epa.gov/environmentaljustice/ej-2020-glossary.

general population. This fact is highly pertinent to the historical legacy of racial and economic discrimination, and the relationship of vulnerability to health disparities.[88]

Failing to consider exposures linked to disposal, legacy uses, associated disposal, and legacy disposal systematically underestimates the background level of exposures faced by many environmental justice communities. In order to determine whether those communities will face an unreasonable risk of injury from the chemicals undergoing risk evaluation, EPA must consider exposures from disposal, legacy uses, associated disposal, and legacy disposal.

13. EPA needs to accurately evaluate real-world occupational and consumer exposures.

A. EPA needs to explain how it will incorporate consideration of engineering controls, personal protective equipment (PPE), and labeling into its analyses.

All but one of the problem formulations state that EPA will "[c]onsider and incorporate applicable engineering controls and/or personal protective equipment into exposure scenarios." *See, e.g.*, Problem Formulation for Perchloroethylene at p. 71; Problem Formulation for DCM at p. 64; Problem Formulation for Asbestos at p. 49; Problem Formulation for 1-BP at p. 66; Problem Formulation for 1,4-Dioxane at p. 49; Problem Formulation for Carbon Tetrachloride at p. 55; Problem Formulation for HBCD at p. 63; Problem Formulation for NMP at p. 57; Problem Formulation for TCE at p. 64. But EPA has provided an inadequate explanation for how EPA will consider this information or what assumptions EPA will make when doing so.

In its response to comments on its earlier Scope Documents, EPA states that: "When appropriate, in the risk evaluation, OPPT will use exposure scenarios both with and without engineering controls and/or PPE that may be applicable to particular worker tasks on a case-by-case basis for a given chemical."[89] As a general rule, at a minimum, EPA should always evaluate each exposure scenario without the engineering controls and PPE unless EPA has solid evidence that the scenario without engineering controls and/or PPE never occurs in the real world. In addition, EPA needs to rely on its information authorities to obtain accurate empirical evidence about how widely these measures are used as well as how effective these measures are at reducing exposure. Absent such evidence, EPA cannot assume that they are widely used or effective.

For example, Kemira submitted a comment letter alerting EPA to certain industrial applications of NMP, and in that letter, Kemira described certain "ideal" PPE worn during the use of the chemical.[90] EPA certainly cannot assume that such use of NMP will be accompanied by "ideal" PPE without strong

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[88] National Environmental Justice Advisory Council, Cumulative Risks/Impacts Work Group, *Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and cumulative Risks/Impacts* at 24 (Dec. 2004), https://www.epa.gov/sites/production/files/2015-04/documents/ensuringriskreducationnejac.pdf (emphasis added).

[89] EPA's Responses to Public Comments Received on the Scope Documents for the First Ten Chemicals for Risk Evaluation under TSCA p.4, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0725-0051.

[90] *See* Comment submitted by Colleen M. Snyder, Manager, Product Stewardship and Regulatory Affairs, Kemira, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0085.

evidence that people always use the relevant PPE. Instead, EPA should prepare a risk evaluation analyzing the risks without "ideal" PPE, since non-ideal scenarios could easily occur in the real world.

B. Even where engineering controls and/or PPE are used to some extent, EPA should always evaluate exposures scenarios without engineering controls and PPE in order to assess exposures and risks to those subpopulations not subject to such controls.

Rarely if ever in the real world will an exposure scenario involve 100% use and efficiency of engineering controls and/or PPE, so EPA always will need to evaluate exposure scenarios both with and without such controls. This is because, under TSCA, EPA is required to evaluate and protect against risk to potentially exposed or susceptible subpopulations including those "who, due to *** greater exposure, may be at greater risk." 15 U.S.C. § 2602(12).

If EPA has reliable affirmative evidence as to the extent of use and efficiency of use of engineering controls and PPE for a given scenario, it may be able to estimate overall exposures arising from the scenario. However, that does not absolve the agency of an obligation to evaluate exposures and risks for the subset of people for whom those controls are not in place or do not reach 100% efficiency.

Absent such empirical evidence, EPA should assume no use of engineering controls or PPE in evaluating exposure, or at least apply reasonable worst-case assumptions as to the extent and efficiency of their use.

EPA should additionally analyze the exposure scenario with engineering controls and/or PPE, to evaluate exposures for the subset of people for whom those controls are in place. In doing so, however, EPA should evaluate exposures resulting from varying efficiencies in exposure reduction achieved by the controls. Such analyses may also be valuable at a later risk management stage.

C. EPA should never rely on labeling and PPE as a basis to assume low or no exposure, given the major real-world limitations of these measures.

EPA should not inaccurately assume that people comply with all warning labels and always use PPE. EDF strongly urges EPA to consider real-world exposures reflecting the reality of the sometimes low-compliance with or non-existence of these measures. EPA should account for such real-world limitations of PPE in the risk evaluations by either collecting or requiring the development of empirical data, or, in their absence, using worst-case assumptions to assess the extent of exposure reduction resulting from labeling and PPE. Procurement and reliance on such data clearly constitute best available science (a requirement under TSCA § 26), and EPA has clear authority to collect or require the development of such data under § 4(b)(2)(A). And absent empirical evidence establishing the extent to which people are using these measures and doing so effectively, EPA should assume that they are or may not be. Indeed, EPA's need for accurate information about actual compliance is another reason to rely on its authorities under TSCA § 8 to mandate that manufacturers and processors provide such information. In addition, it bears noting that reliance on PPE as a primary measure to protect workers is counter to OSHA's Industrial Hygiene Hierarchy of Controls (HOC), a long-standing principle that prioritizes measures to eliminate or reduce the presence of a hazard in occupational settings (e.g.,

substitution/use of less toxic chemicals and institution of engineering controls) over measures that shift burdens onto the workers themselves, such as through reliance on PPE and warning labels. The HOC exemplifies the best available science for creating safe, healthful workplace environments.

In comments EDF has submitted in these dockets, EDF previously commented on the serious limitations of labeling and PPE, as well as the importance of adherence to the hierarchy of controls to limit workplace exposures.[91] EDF incorporates and reiterates the points made in those comments here.

14. Assessment factors do not lead to conservative calculations; in fact, assessment factors account for real-world sources of variability as well as database limitations.

In the problem formulations, EPA often states that it used a "conservative approach" and "conservative assumptions" when assessing aquatic environmental exposures. *See, e.g.*, Problem Formulation for 1,4-Dioxane at p. 29. These statements at least in part appear based on EPA's use of assessment factors (AFs) in developing the concentrations of concern (COCs). In fact, AFs account for real-world sources of variability as well as database limitations, and cannot be construed as "safety factors" that yield conservative estimates. As EPA acknowledges: "The application of AFs provides a lower bound effect level that would likely encompass more sensitive species not specifically represented by the available experimental data. AFs are also account for differences in inter- and intra-species variability, as well as laboratory-to-field variability." *Id*. at 70.

The National Academy of Sciences, in its 2009 report titled *Science and Decisions: Advancing Risk Assessment* has this to say on this subject, albeit in the context of human rather than environmental health:

> Another problem *** is that the term *uncertainty factors* is applied to the adjustments made to calculate the RfD [reference dose, derived from, e.g., a no-effect level] to address species differences, human variability, data gaps, study duration, and other issues. The term engenders misunderstanding: groups unfamiliar with the underlying logic and science of RfD derivation can take it to mean that the factors are simply added on for safety or because of a lack of knowledge or confidence in the process. That may lead some to think that the true behavior of the phenomenon being described may be best reflected in the unadjusted value and that these factors create an RfD that is highly conservative. But the factors are used to adjust for differences in individual human sensitivities, for humans' generally greater sensitivity than test animals' on a milligrams-per-kilogram basis, for the fact that chemicals typically induce harm at lower doses with longer exposures, and so on. At times, the factors have been termed *safety factors*,

[91] *See, e.g.*, EDF Comments on TSCA Review and Scoping for First 10 Chemicals under the Lautenberg Act at 6 (Mar. 15, 2017), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0736-0046; EDF Comments on Significant New Uses of Chemical Substances; Updates to the Hazard Communication Program and Regulatory Framework; Minor Amendments to Reporting Requirements for Premanufacture Notices (Nov. 21, 2016), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2014-0650-0052.

> which is especially problematic given that they cover variability and uncertainty and are not meant as a guarantee of safety.[92]

In evaluating risks, EPA should recognize that AFs ensure greater accuracy and do not provide a safety factor rendering the evaluation "conservative."

15. EPA's discussion of its systematic review methodology is insufficiently explained and suggests that EPA is taking an approach to the evidence that violates TSCA §§ 26(i) and 26(h).

In the problem formulations, EPA states that it will rely on data and studies that meet the "systematic review" data quality criteria.

> Human health hazards from acute and chronic exposures will be identified by evaluating the human and animal data that meet the systematic review data quality criteria described in the Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018) document. *** Hazards identified by studies *meeting data quality criteria* will be grouped by routes of exposure relevant to humans (oral, dermal, inhalation) and by cancer and noncancer endpoints.

Problem Formulation for TCE at p. 69 (emphases added); *see also* Problem Formulation for 1-BP at p. 69; Problem Formulation for 1,4-Dioxane at p. 51; Problem Formulation for Carbon Tetrachloride at p. 57; Problem Formulation for HBCD at p. 71; Problem Formulation for DCM at p. 68; Problem Formulation for NMP at p. 60; Problem Formulation for Perchloroethylene at p. 75.

EPA has not explained, either here or in its OCSPP Systematic Review document, what it means for data or studies to "meet the systematic review data quality criteria." EPA must do so.

Moreover, this language suggests EPA will apply its data quality criteria in a black-or-white manner: a study is either in or out. How is this consistent with the statute's requirement that EPA take a weight-of-evidence approach? How is it consistent with the scientific standards in TSCA section 26(h), which require EPA to consider the "extent" or "degree" to which various factors characterize information, methods, models, etc. – which does not support the black-or-white approach EPA appears to intend to apply. EDF has previously explained that TSCA §§ 26(h) and 26(i) contemplate EPA weighing various information, see Appendix A at 55-57, and EPA should implement those requirements consistent with that approach.

16. EPA's description of systematic review is scientifically flawed and needs extensive revision to align with best practices and leading systematic review approaches.

EPA's description of systematic review in the problem formulations is wholly deficient. Specifically, EPA describes systematic review as follows: "EPA/OPPT generally applies a systematic review process and workflow that includes: (1) data collection, (2) data evaluation and (3) data integration of the scientific

[92] NAT'L RESEARCH COUNCIL, SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT at chp. 5, p. 132 (2009), https://www.ncbi.nlm.nih.gov/pubmed/25009905 (emphases in original).

data used in risk evaluations developed under TSCA." Problem Formulation for Asbestos at p. 13; Problem Formulation for 1-BP at p. 15; Problem Formulation for 1,4-Dioxane at p. 14; Problem Formulation for Carbon Tetrachloride at p. 15; Problem Formulation for HBCD at p. 16; Problem Formulation for DCM at p. 17; Problem Formulation for NMP at p. 14; Problem Formulation for PV 29 at p. 11; Problem Formulation for Perchloroethylene at p. 18; Problem Formulation for TCE at p. 16.

A. EPA fails to address protocol development, which is a fundamental component of systematic review.

A major deficiency in this description of EPA's systematic review approach, and in its related OCSPP Systematic Review document, is the complete absence of protocol development—a fundamental component of systematic review.

As noted in the 2014 National Academy of Sciences (NAS) report that reviewed EPA's IRIS program:

> Critical elements of conducting a systematic review include formulating the specific question that will be addressed (problem formulation) and *developing the protocol* that specifies the methods that will be used to address the question (protocol development).[93]
>
> After the systematic-review questions are specified, protocols for conducting the systematic reviews to address the questions should be developed. *A protocol makes the methods and the process of the review transparent, can provide the opportunity for peer review of the methods, and stands as a record of the review.* It also minimizes bias in evidence identification by ensuring that inclusion of studies in the review does not depend on the studies' findings. Any changes made after the protocol is in place should be transparent, and the rationale for each should be stated. EPA should include protocols for all systematic reviews conducted for a specific IRIS assessment as appendixes to the assessment.[94]

EPA's IRIS program reflects this NAS recommendation by developing problem formulation and assessment protocols for each of its assessments.[95] OCSPP needs to develop full protocols for each of its risk evaluations, and should consult with the IRIS program on how best to do so in consideration of requirements under TSCA.

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[93] Nat'l Research Council, *Review of EPA's Integrated Risk Information System (IRIS) Process* at p. 5 (2014), https://www.ncbi.nlm.nih.gov/books/NBK230060/ (emphasis added).
[94] *Id.* at 6 (emphases added).
[95] U.S. EPA, Office of Research & Dev., National Academy of Science Committee to Review Advances Made to the IRIS Program at slide 23 (Feb. 2018), http://nas-sites.org/dels/files/2018/01/AdIRIS-15.pdf.

B. EPA fails to describe its approach to evidence integration (weight of evidence) despite claims that it has done so in the problem formulation.

EPA has also failed to describe its approach to evidence integration at all. In multiple instances, EPA points to its OCSPP Systematic Review document as providing more information on how it plans to conduct evidence integration. For example, EPA states:

> Evaluate the weight of the evidence for consumer exposures. EPA will rely on the weight of the scientific evidence when evaluating and integrating data related to consumer exposure. The weight of the evidence may include qualitative and quantitative sources of information. The data integration strategy will be designed to be fit-for-purpose in which EPA will use systematic review methods to assemble the relevant data, evaluate the data for quality and relevance, including strengths and limitations, followed by synthesis and integration of the evidence. *Refer to the Application of Systematic Review in TSCA Risk Evaluations (U.S. EPA, 2018) document for more information on the general process for data integration.*

Problem Formulation for TCE at p. 65 (emphasis added); *see also*, *e.g.*, Problem Formulation for Asbestos at p. 52; Problem Formulation for 1-BP at p. 59; Problem Formulation for 1,4-Dioxane at p. 49; Problem Formulation for Carbon Tetrachloride at pp. 54-57; Problem Formulation for HBCD at pp. 60, 68, 70, 71; Problem Formulation for DCM pp. 62-66; Problem Formulation for NMP at p. 60; Problem Formulation for Perchloroethylene at p. 67.

In fact, EPA has not described its approach to data (evidence) integration in any of its problem formulations, nor in its OCSPP Systematic Review document. Indeed, OCSPP has not described its approach to evidence integration anywhere. Instead, it appears that EPA intends to do so in each individual draft chemical risk evaluation and in the absence of a protocol established up front. This approach is hugely problematic, lending itself to bias and inconsistency in how EPA conducts weight of evidence across risk evaluations. EPA should describe its general approach to evidence integration in a revised systematic review methodology document and then incorporate that into specific protocols it develops for each risk evaluation (see EDF's comments on EPA's OCSPP Systematic Review document).

* * * * *

More broadly, in revising its approach to conducting systematic review, we recommend that OCSPP consult with IRIS, the National Toxicology Program's Office Health Assessment and Translation, and other leading experts on the application of systematic review for chemical assessment, as discussed further in EDF's comments on EPA's OCSPP Systematic Review document.[96]

[96] EDF Comments on Application of Systematic Review in TSCA Risk Evaluations (Aug. 16, 2018), https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0210.

17. EPA's vague description of its intended approach to dose-response modeling lacks sufficient explanation and scientific justification.

In eight of the problem formulations, in describing how it expects to analyze human health hazards, EPA states:

> Hazard data will be evaluated to determine the type of dose-response modeling that is applicable. Where modeling is feasible, a set of dose-response models that are consistent with a variety of potentially underlying biological processes will be applied to empirically model the dose-response relationships in the range of the observed data consistent with the EPA Benchmark Dose Technical Guidance Document.

Problem Formulation for 1-BP at p. 69; Problem Formulation for 1,4-Dioxane at p. 51; Problem Formulation for Carbon Tetrachloride at p. 58; Problem Formulation for HBCD at p. 72; Problem Formulation for DCM at p. 68; Problem Formulation for NMP at p. 60; Problem Formulation for Perchloroethylene at p. 75; Problem Formulation for TCE at p. 69.

For many chemicals, the biological processes underlying observed effects are not well understood or may not be understood at all. This is the case even for pharmaceuticals available on the market today. The National Research Council wrote in its 2014 report, *Review of EPA's Integrated Risk Information System (IRIS) Process*, that "if FDA were required to organize drug safety around mechanism, it would be nearly impossible to regulate many important drugs because the mechanism is often not understood, even for drugs that have been studied extensively."[97] Indeed, an earlier 2010 Nature Medicine editorial noted:

> It is true that we use many highly prescribed drugs without a clear idea of how they work—which targets they hit, what processes they alter and which of these actions are required for therapeutic efficacy. For instance, lithium, used to treat bipolar disorder, modulates many molecular targets, but which—or how many—of these are required for its beneficial effects is uncertain.[98]

EPA should fully describe how it intends to approach dose-response modeling in the absence of sufficient knowledge underlying biological processes, as will be the case with endpoints associated with numerous chemicals EPA evaluates. For example, in the context of trichloroethylene, the mechanistic

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[97] Nat'l Research Council, *Review of EPA's Integrated Risk Information System (IRIS) Process* at chp. 6, p. 90 (2014), https://www.ncbi.nlm.nih.gov/books/NBK230065/.

[98] Editorial, *Mechanism Matters*, 16:4 Nature Med. 347 (Apr. 2010), https://www.nature.com/articles/nm0410-347.pdf.

basis for the identified association with Parkinson's disease is not yet fully understood,[99] yet there is compelling scientific evidence demonstrating the association.[100]

More broadly, EPA must employ health-protective approaches to dose-response modeling, as described at length in the National Academy of Sciences (NAS) report, *Science and Decisions: Advancing Risk Assessment*.[101] Among other recommendations, the NAS argued that "***cancer and noncancer responses [to chemical exposures] be assumed to be linear as a default****."[102]

18. EPA's must consider acute exposures in evaluating developmental effects.

In all but one of the problem formulations, EPA uses this or similar language:

> When conducting the risk evaluation, the relevance of each hazard within the context of a specific exposure scenario will be judged for appropriateness. *For example, hazards that occur only as a result of chronic exposures may not be applicable for acute exposure scenarios*. This means that it is unlikely that every hazard identified in the scope document will be considered for every exposure scenario.

Problem Formulation for TCE at p. 39 (emphasis added); *see also* Problem Formulation for Asbestos at p. 33; Problem Formulation for 1-BP at p. 41; Problem Formulation for 1,4-Dioxane at p. 32; Problem Formulation for Carbon Tetrachloride at p. 39; Problem Formulation for HBCD at p. 40; Problem Formulation for DCM at p. 41; Problem Formulation for NMP at p. 38; Problem Formulation for Perchloroethylene at p. 48.

EPA's proposal here is deeply concerning, and suggests that the agency plans to ignore its own established guidance[103] on the evaluation of chemical hazards and risks.

We will illustrate these concerns with an example for TCE. EPA's 2011 Integrated Risk Information System (IRIS) assessment[104] correctly identified fetal cardiac malformation, a developmental toxicity effect, as the most sensitive endpoint and supported by multiple lines of evidence—epidemiological, laboratory animal, metabolism, and mechanistic studies. EPA OCSPP reaffirmed this conclusion in its

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[99] Edward A. Lock, et al., *Solvents and Parkinson disease: A systematic review of toxicological and epidemiological evidence*, 266:3 TOXICOLOGY & APPLIED PHARMACOLOGY 345 (Feb. 2013), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3621032/.

[100] U.S. EPA, Office of Research & Dev., *Toxicological Review of Trichloroethylene Appendix D* (Sept. 2011), https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/Appendix_D_0199tr.pdf.

[101] NAT'L RESEARCH COUNCIL, SCIENCE AND DECISIONS: ADVANCING RISK ASSESSMENT (2009), https://www.ncbi.nlm.nih.gov/books/NBK214630/.

[102] *Id.* at chp. 5, p. 180.

[103] *See* U.S. EPA, *Guidelines for Developmental Toxicity Risk Assessment* (Dec. 1991), https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf.

[104] U.S. EPA, *Toxicological Review of Trichloroethylene (CAS No. 79-01-6) In Support of Summary Information on the Integrated Risk Information System (IRIS)* (Sept. 2011), https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf.

2014 TCE work plan risk assessment.[105] The TCE problem formulation introduces the possibility that EPA may exclude developmental toxicity as an acute effect—a decision that would not only be odds with EPA's past assessments, proposed regulations, and guidance but also at odds with applying a health-protective approach to chemical risk evaluation.

As described in EPA's proposed section 6 proposed TCE rules[106,107] and in the 2014 TCE risk assessment, EPA relied on developmental endpoints for assessing health risks of TCE resulting from acute exposure. This is in alignment with EPA's longstanding agency-wide guidance, Guidelines for Developmental Toxicity Risk Assessment,[108] which indicates that even a single exposure to a chemical within a critical window of development may produce adverse developmental effects. For example, EPA's proposed section 6 TCE rule, Trichloroethylene (TCE) Regulation of Use in Vapor Degreasing Under TSCA Section 6(a), states:

> As indicated in the TCE risk assessment, EPA's policy supports the use of developmental studies to evaluate the risks of acute exposures. This science-based policy presumes that a single exposure of a chemical at a critical window of fetal development may produce adverse developmental effects (Ref. 5). This is the case with cardiac malformation. EPA reviewed multiple studies for suitability for acute risk estimation including a number of developmental studies of TCE exposure and additional developmental studies of TCE metabolites (Appendix N) (Ref. 2). EPA based its acute risk assessment on the most sensitive health endpoint (i.e., fetal heart malformations) representing the most sensitive human life stage (i.e., the developing fetus) (Ref. 2).[109]

EPA needs to follow this established EPA risk assessment practice, and include developmental toxicity effects in its assessment of acute exposure from chemicals. In the case of TCE, EDF strongly recommends that the agency include fetal cardiac malformations in its assessment of acute effects in addition to its assessment of chronic effects. EPA has provided no basis for deviating from this practice in its problem formulation, and to do so would deviate from using the best available science as required under TSCA.

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[105] US EPA, Office of Chemical Safety and Pollution Prevention. "TSCA Work Plan Chemical Risk Assessment. Trichloroethylene: Degreasing, Spot Cleaning and Arts & Crafts Uses." June 2014. EPA Document #740-R1-4002. Available: https://www.epa.gov/sites/production/files/2014-11/documents/tce_opptworkplanchemra_final_062414.pdf.

[106] Trichloroethylene; Regulation of Certain Uses Under TSCA § 6(a), 81 Fed. Reg. 91592, 91595, 91599 (proposed Dec. 16, 2016), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0163-0001.

[107] Trichloroethylene (TCE); Regulation of Use in Vapor Degreasing Under TSCA Section 6(a), 82 Fed. Reg. 7432, 7435, 7439 (proposed Jan. 19, 2017), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0387-0001.

[108] U.S. EPA, *Guidelines for Developmental Toxicity Risk Assessment* at 4, 45 (Dec. 1991), https://www.epa.gov/sites/production/files/2014-11/documents/dev_tox.pdf.

[109] Trichloroethylene (TCE); Regulation of Use in Vapor Degreasing Under TSCA Section 6(a), 82 Fed. Reg. 7432, 7439 (proposed Jan. 19, 2017), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0387-0001.

More broadly, EPA must closely examine any effect it believes to arise only from chronic exposures to determine whether in fact this is true across the diverse human population, including where potentially exposed or susceptible subpopulations may be at increased risk for effects after shorter periods of exposure compared to the general population.

19. Where EPA adopts a tiered approach to exposure analyses, EPA must not repeat the errors from its cursory dismissals of certain exposures.

In a number of the problem formulations, EPA indicates it plans to use a tiered approach in further analyzing exposure scenarios. *See, e.g.*, Problem Formulation for 1-BP at p. 63; Problem Formulation for NMP at p. 58; Problem Formulation for Asbestos at p. 73; Problem Formulation for HBCD at p. 67. Throughout our comments, EDF has criticized aspects of EPA's exposure analyses used to decide it will not conduct further analysis and its rush to judgment that certain exposures pose no unreasonable risk. These concerns, addressed in our chemical-specific comments, include (but are not limited to):

- equating a lack of information to mean there is no or low exposure;
- questionable characterization of models or assumptions as conservative;
- assertions of low exposure based on EPA "expectations" that are insufficiently justified or documented;
- dismissal of serious data gaps with no plan to fill them and instead resorting to modeling or use of data on surrogate chemicals; and
- reliance on unverified or very limited information sources to make sweeping conclusions.

To the extent that EPA's reference to using a tiered approach to exposure analysis going forward indicates EPA plans to conduct and rely on the same types of cursory analyses, these same critiques will apply and EPA's use of such analysis to discard additional exposures scenarios will be equally arbitrary and inconsistent with TSCA's requirement that EPA use the best available science.

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COMMENTS ON SPECIFIC PROBLEM FORMULATIONS

Comments on Asbestos

EDF has raised numerous serious concerns about this problem formulation throughout these comments (search for "asbestos" to locate them). Here we provide a few additional comments specific to this problem formulation.

20. EPA has unreasonably excluded conditions of use of asbestos.

In the asbestos problem formulation, EPA states that it will exclude "legacy uses, associated disposals, and legacy disposals" from the risk evaluation. U.S. EPA, Problem Formulation of the Risk Evaluation for Asbestos at p. 8 (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0736-0131. As EDF previously explained in its comments on the scope, EPA cannot rationally exclude so-called legacy uses and associated disposals. EDF incorporates and reiterates those points here as well. EDF Comments on Ten Scopes under the Toxic Substances Control Act pp.8-9, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0743-0069. For the same reasons, EPA cannot rationally exclude so-called legacy disposals. Along with other petitioners, EDF has further developed these arguments in a Brief which is attached as Appendix A. EDF incorporates and reiterates those points here. *See* Appendix A at p. 40-51.

21. Even if EPA promulgates the asbestos SNUR it recently proposed, EPA must still analyze the conditions of use it addressed and the resulting exposures and risks in its risk evaluation of asbestos.

EPA recently proposed a Significant New Use Rule (SNUR) addressing certain conditions of use of asbestos where manufacturing and processing for those uses are no longer ongoing in the United States. 83 Fed. Reg. 26,922 (June 11, 2018). EDF filed comments on this proposal, which we incorporate and reiterate here. EDF Comments on Asbestos; Significant New Use Rule, https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0159-1269. As EDF noted in those comments, EPA's promulgation of this SNUR is a needed stopgap measure.

The proposed SNUR includes factual findings that support analyzing the conditions of use identified in the proposal as part of this risk evaluation. EPA acknowledged that "non-friable asbestos-containing building materials can release fibers if disturbed during building repair or demolition." 83 Fed Reg. 26,922, 26,927 (June 11, 2018) (citing 40 C.F.R. part 61, subpart M, Asbestos National Emission Standards for Hazardous Air Pollutants (NESHAP)). Thus, EPA acknowledged that these existing conditions of use continue to result in exposures and present a significant risk to the public, so EPA should be analyzing those exposures and risks in its risk evaluation. Notably, ignoring this evidence would be irrational and arbitrary because it leads to overlooking real-world risks.

As EPA noted, absent the proposed SNUR, these conditions of use could resume "at any time, without prior notice to EPA." *Id.* However, promulgation of that SNUR would not justify EPA's decision to ignore those conditions of use in its risk evaluation of asbestos. As noted above, EDF has previously articulated that EPA must consider *all* conditions of use when preparing a risk evaluation under TSCA § 6. A SNUR does not change the statutory requirement that EPA consider *all* conditions of use in its risk evaluations, especially because a SNUR does not permanently foreclose any conditions of use. A SNUR is not a ban on a condition of use, and indeed, the TSCA § 5 process contemplates that persons can submit significant new use notices with the intent of engaging in the significant new use in the future. Thus, these significant new uses remain reasonably foreseen, and only a subsequent order or rule issued by EPA following its review of a SNUN could foreclose such a condition of use.

Moreover, the existence of the SNUR does not change the fact that these conditions of use are "known" to have occurred in the past, and these conditions of use are definitely "reasonably foreseen." 15 U.S.C. § 2602(4). Congress included "reasonably foreseen" circumstances within TSCA with the express goal of ensuring that EPA swept more broadly than known (or intended) uses; EPA cannot evade that duty by limiting its analysis to conditions of uses with evidence of current, ongoing use—such an interpretation would effectively limit EPA's analysis to "known" uses. Reasonably foreseen is a term of art with a long history in the law; it is well established under the law that "[a] natural and probable consequence is a foreseeable consequence. But to be reasonably foreseeable [t]he consequence need not have been a strong probability; a possible consequence which might reasonably have been contemplated is enough." *People v. Medina*, 209 P.3d 105, 110 (Cal. 2009) (internal citations and quotation marks omitted). Numerous courts have recognized that circumstances are reasonably foreseen when similar circumstances have occurred in the past. *See, e.g., McKown v. Simon Prop. Grp., Inc.*, 344 P.3d 661, 663 (Wash. 2015); *Burns v. Penn Cent. Co.*, 519 F.2d 512, 515 (2d Cir. 1975). The fact that these conditions of use occurred in the past establishes that they are reasonably foreseen. And in the SNUR, EPA acknowledged that "the importing or processing of asbestos (including as part of an article) for the significant new uses proposed in this rule may begin at any time." 83 Fed. Reg. at 26,927.

Hence, even if EPA promulgates the asbestos SNUR it recently proposed, EPA must still analyze the conditions of use the SNUR addressed and the resulting exposures and risks in its risk evaluation of asbestos.

Comments on 1-Bromopropane

22. EPA has excluded or failed to sufficiently identify and analyze relevant conditions of use, exposure pathways, hazards, and vulnerable subpopulations for 1-Bromopropane.

A. EPA has provided insufficient justification for its exclusion of certain activities from the risk evaluation based on not being conditions of use or not being expected to occur.

EPA plans to exclude certain uses of 1-bromopropane (1-BP) from the risk evaluation by concluding the activities should not be considered conditions of use:

Agricultural non-pesticidal industrial/commercial/consumer use: EPA provides only a single statement with no relevant reference as the basis for this exclusion:

> Based on information available to EPA, EPA determined that 1-BP is not used in agricultural products (non-pesticidal), only in the processing of such products.

U.S. EPA, Problem Formulation of the Risk Evaluation for 1-Bromopropane at p. 19 (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0741-0067. The only source EPA cites (in Table 2-2) is the data EPA collected in 2016 under the Chemical Data Reporting (CDR) rule. This source indicates that a company in fact reported domestic manufacture of 1-BP for "industrial processing and use" in the "Pesticide, fertilizer, and other agricultural chemical manufacturing" sector, and further reported it accounted for 25% of its total production. Several questions remain:

First, EPA provides no indication of how it determined that 1-BP is "not used in agricultural products (non-pesticidal), only in the processing of such products." As written, this stands as a mere assertion by EPA.

Second, the activity reported in the CDR is clearly a "condition of use" of 1-BP, which is reported as being manufactured for this very purpose, and EPA has no basis to exclude such a condition of use simply because it entails downstream processing of agricultural products (non-pesticidal) by others, rather than being an ingredient in such products. Processing is itself a condition of use.

Third, while the CDR data indicate the chemical is an intermediate and processed as a reactant, EPA has not provided any data demonstrating unreacted 1-BP is not present in the final product as a residual.

Fourth, even were EPA to establish that 1-BP is not present as a residual in non-pesticidal agricultural products, that is no basis for a wholesale exclusion from the risk evaluation of all of the activities associated with 1-BP in this sector, including worker exposures, environmental releases, etc.

Finally, as EPA well knows, CDR reporting is subject to numerous limitations, including volume thresholds and reporting exemptions that preclude EPA from relying solely on it to conclude manufacturing or processing for a particular use is not occurring.

EPA has provided an inadequate rationale for excluding this condition of use; EPA should analyze this condition of use in the risk evaluation.

Consumer use of adhesives (except as an adhesive accelerant for arts and crafts), engine degreasing, and brake cleaning: EPA's only rationale for these exclusions is as follows:

> A review of the use of 1-BP as a solvent in adhesives, engine degreasers, and in brake cleaners showed that these uses of 1-BP are not consumer uses, except as an adhesive accelerant in arts and crafts. In all other uses of 1-BP as an adhesive, 1-BP-containing adhesives are sold through wholesale channels for commercial and industrial uses, and usually in amounts larger than consumers could use. 1-BP has never been advertised (or used) as a consumer brake cleaner or engine degreaser. ... Also, consumers will avoid the use of 1-BP as an engine degreaser or brake cleaner because 1-BP is expensive. In general, heavy duty degreasers containing 1-BP are twice the cost of other heavy duty degreasers and five times the cost of other available consumer brake cleaners. (pp. 19-20)

EPA's problem formulation fails to provide adequate support for these exclusions.

First, no sources or supporting data are cited or provided. In the accompanying Table 2-2, the only sources EPA lists, purportedly to support these exclusions, in fact do the opposite.

- For adhesives, EPA cites two sources: First, its 2016 draft Work Plan Risk Assessment for 1-BP, which was in large part driven by concerns over just such consumer uses. Second, EPA also cites a March 2017 letter submitted to EPA by EnviroTech, which clarifies that 1-BP is used as a carrier for adhesives, but does not address the assertions about consumer use, wholesale vs. retail sales, or advertising that EPA makes.[110]

[110] The Enviro Tech letter does state, however:

> The use of nPB [n-propyl bromide, a synonym for 1-BP] in the Adhesive sector has a *sad history of over-exposure of workers*. In June, 2007, USEPA proposed to find nPB as unacceptable for use in the Adhesive, Coatings and Inks sector. Enviro Tech, along with the vast majority of our competitors and suppliers, have publically supported this proposed SNAP rule [issued under EPA's Significant New Alternatives Policy (SNAP) program, which identifies substitutes to ozone-depleting chemicals]. Unfortunately, USEPA has seen fit, without further comment, to leave the rule as only proposed by *not issuing a final rule for ten years.* After discussing the health effects of nPB in over 35 pages of text in the rule and proposed rules published ion [*sic*] 2007, we cannot understand why the USEPA would leave a rule in limbo for ten years, despite having the support of the industry that would be regulated by that rule. USEPA immediately issuing a final rule under SNAP would address an important concern shard by the industry and USEPA as noted in its TSCA documents on nPB. (p. 3, emphases added)

This excerpt is telling in that it notes that adhesive use of 1-BP remains a major concern and has not been addressed through existing regulatory authorities.

- For brake cleaners or engine degreasers, EPA cites only its own 2017 use document, "Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: 1-Bromopropane," ("Use document") which prominently identifies the very uses EPA now plans to exclude.

Based on EDF's own search of the docket, we located a document posted by EPA but not cited in the problem formulation for brake cleaners or engine degreasers.[111] The document, dated February 2018, purports to support EPA's assertion that 1-BP-containing brake cleaners and engine degreasers are not used by consumers. It consists of two short paragraphs of "analysis" based on a single company's "product guide." The analysis makes numerous assumptions and leaps of logic in its effort to sweepingly conclude that consumers never purchase and use 1-BP-containing brake cleaners or engine degreasers, largely built on questionable notions of consumers' preferences and knowledge.

It is indeed worth highlighting that even EPA states: "It should be noted that some consumers may purchase and use products primarily intended for commercial use." (p. 49) Yet EPA plans to omit such uses entirely.

Second, EPA's own current problem formulation contradicts itself. On p. 10 EPA states:

> Consumers and bystanders may be exposed to 1-BP from various consumer uses such as *aerosol and spray adhesives*, aerosol spot removers and aerosol *cleaning and degreasing products.* For 1-BP, EPA considers workers, occupational non-users, consumers, bystanders, and certain other groups of individuals who may experience greater exposures than the general population due to proximity to conditions of use to be potentially exposed or susceptible subpopulations. (p. 10, emphases added)

Third, even if EPA has evidence these uses are not currently ongoing, on what basis can it conclude the uses are not "reasonably foreseen"? Such uses have not been banned (that could be done through a rulemaking pursuant to the current risk evaluation). Nor is there any serious structural, economic or technical rationale EPA has provided for why they could not resume. As discussed in detail earlier in the comments (see Section 4.A), EPA must assume that past uses, absent a regulatory ban, are reasonably foreseen and include them in its risk evaluations.

Interestingly, EPA itself makes an argument for the potential for a different use of 1-BP to return or increase. It does so when discussing, in this same section of the problem formulation, the use of 1-BP in dry cleaning:

> EPA currently believes that few dry cleaners use 1-BP as a dry cleaning solvent. *** However, *the use of 1-BP in the dry cleaning industry remains a reasonably foreseen condition of use.* EPA is currently evaluating tetrachloroethylene (perc) under TSCA, and

[111] *See* EPA-HQ-OPPT-2016-0741-0065.

> if EPA were to restrict the use of perc in dry cleaning, many dry cleaners might use 1-BP in their machines *absent regulatory restrictions from doing so.*" (p. 20, emphases added)

This logic – that other events could later alter the extent of use of a chemical – is among the reasons why Congress required EPA to include "reasonably foreseen" conditions of use in its risk evaluations under TSCA. The same logic should have been extended to other uses EPA intends to exclude altogether.

In sum, EPA has provided inadequate and contradictory reasons for excluding the consumer uses of 1-BP as a solvent in adhesives, engine degreasers, and in brake cleaners. EPA should analyze these conditions of use in the risk evaluation.

Consumer disposal of consumer products: EPA plans not to analyze this activity based on an unsupported assumption that exposure from this activity is not expected. EPA states:

> EPA does not expect exposure to consumers from disposal of consumer products. It is anticipated that most products will be disposed of in original containers, particularly those products that are purchased as aerosol cans. Liquid products may be recaptured in an alternate container following use (refrigerant flush or coin cleaning). (p. 39, repeated verbatim on p. 50)

EPA provides no evidence to support its expectation and anticipation. In addition, in the last sentence EPA also contradicts itself about the potential for consumer exposure; the uses it identifies as potentially involving "recapture[] in an alternative container following use" – refrigerant flush and coin cleaning – are both listed as consumer uses in Table 2-3. Consumer collection and disposal of spent 1-BP after these uses, even if done in a different container, may well lead to consumer exposures. EPA should analyze the potential exposure to consumers from disposal of consumer products.

B. Major deficiencies abound in EPA's assertion that exposures to 1-BP falling under other legal jurisdictions are adequately managed.

We have discussed earlier (see Section 5) the many legal flaws in EPA's assertion that it can ignore exposure pathways that fall under other EPA authorities and assume they "adequately assess and effectively manage" any risks. EPA's 1-bromopropane problem formulation also contains technical and scientific flaws or inaccuracies that result in EPA's failure to adequately justify on scientific grounds the sweeping exposure pathway exclusions it has proposed. To illustrate, we provide below some specific comments on examples of unsupported or insufficiently supported statements in the document.

Exclusion of landfill releases: EPA states:

> 1-BP migration to groundwater from RCRA Subtitle C landfills or RCRA Subtitle D municipal landfills regulated by the state / local jurisdictions to groundwater *will likely be mitigated* by landfill design (double liner, leachate capture for RCRA Subtitle C landfills and single liner for RCRA Subtitle D municipal landfills) and requirements to

> adsorb liquids onto solid adsorbent and containerize prior to disposal. (p. 32, emphasis added)

Reflected perhaps in the conditional language it uses ("will *likely* be mitigated"), EPA neither provides nor cites any data or analysis to support this sweeping assertion. Where authority is or can be delegated to states, as is the case with the Resource Conservation and Recovery Act (RCRA), differential state enforcement of laws and regulations can mean that the actual extent of protection from risks can vary greatly; see Section V.I. A 2011 report from EPA's Office of the Inspector General extensively documented insufficient EPA oversight of state enforcement as well as large state-to-state variations.[112]

Later in the problem formulation, EPA drops even the conditional language and asserts unequivocally as to the adequacy of existing disposal regulations – yet still fails to provide any supporting data or analysis. For example, on p. 34 EPA states without qualification: "EPA will not further analyze releases to hazardous waste landfills because these types of landfill mitigate exposure to the wastes."

Overstating of 1-BP's regulation as hazardous waste: In its zeal to rely on RCRA to exclude all disposal-related exposure pathways, EPA glosses over important distinctions in how hazardous wastes are identified under RCRA. In its general introductory discussion of applicable regulations, EPA states:

> Some industrial and commercial users use 1-BP as a general degreaser because chlorinated solvents are listed hazardous wastes under RCRA, *whereas 1-BP is not, and therefore waste containing 1-BP may not be hazardous* depending on the characteristics of the overall waste stream. (p. 20, emphasis added)

Later, however, when seeking to justify its exclusions, EPA gets rather more definitive:

> Solid wastes containing 1-BP may be regulated as a hazardous waste under the RCRA waste code D001 (ignitable liquids, 40 CFR 261.21). (p. 32)

And still later it gets even more definitive (and more inaccurate):

> 1-BP is regulated as a hazardous waste, waste code D001 (ignitable liquids, 40CFR 261.21). (p. 54)

Finally, buried in an appendix, EPA acknowledges:

> Currently, 1-BP is not regulated under federal regulations as a hazardous waste. (p. 92)

1-BP is not in fact listed as a hazardous waste under RCRA and would only be identified as one if it was disposed of in high enough concentrations to meet the characteristic of "ignitability." Yet EPA has repeatedly and inaccurately invoked disposal of 1-BP as subject to RCRA hazardous waste regulations.

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[112] U.S. EPA, Office of Inspector General, *EPA Must Improve Oversight of State Enforcement* (Dec. 2011), https://www.epa.gov/sites/production/files/2015-10/documents/20111209-12-p-0113.pdf.

EPA should analyze the exposures resulting from disposal of 1-BP based on real scientific evidence.

Vague references to further regulation-based exclusions to come: Even where it does not intend – or at least has not yet expressed its intention – to exclude an exposure pathway or condition of use, EPA vaguely indicates it plans to further consider statutory or regulatory factors to decide whether release or exposure is unlikely or to modify exposure scenarios based on such factors. Again, no detail is provided. For example:

EPA states:

> Information from various EPA statutes (including, for example, regulatory limits, reporting thresholds, or disposal requirements) may be used to assess releases. EPA may determine that a condition of use is *unlikely to result in release* to a particular media based on existing chemical-specific regulations *even though an Emission Scenario or EPA Generic Scenario document indicates a likely release* to that same media. (p. 59, emphases added)

How EPA intends to accomplish these tasks is left a mystery. Moreover, EPA's one-directional statement that it "may determine that a condition of use is unlikely to result in release" based on existing regulations reveals its clear bias: Could not the converse – that the inadequacy of existing regulations makes it likely there will be releases – also be the case?

EPA goes on to state: "EPA will further consider the applicability of EPA regulations to 1-BP during the development of the risk evaluation." (p. 59) This statement suggests more exclusions or conclusions of no or negligible release or exposure are to come. Just what regulations EPA is referring to is far from clear however, especially since two pages later EPA notes how few there actually are for 1-BP: "1-BP is not listed on the TNSSS (Targeted National Sewage Sludge Survey), DMR (Discharge Monitoring Report), or as one of the 189 Hazardous Air Pollutants (HAPs) under Section 112(b) of the Clean Air Act. There are no specific EPA regulations regarding drinking water health advisories, ambient water quality criteria, or effluent level guidelines." (p. 61)

As discussed above in Section 6, EPA should analyze real-world exposures and not assume perfect compliance with existing regulatory limits, to the extent they do exist.

With regards to occupational exposures, EPA states:

> EPA will evaluate and consider applicable regulatory and non-regulatory exposure limits. ... OSHA has not established any occupational exposure limits for 1-BP. However, the American Conference of Governmental Industrial Hygienists (ACGIH) has adopted a recommended Threshold Limit Value (TLV) of 0.1 ppm based on a time-weighted average (TWA) over an 8-hour workday. *EPA will consider the influence of the recommended exposure limits on occupational exposures in the occupational exposure assessment*." (p. 64, emphasis added)

Here again, EPA provides no indication how it will "consider the influence of the recommended exposure limits" – which are voluntary and lack the force of law. EPA is charged with evaluating real-world exposures and should not assume compliance with voluntary exposure guidelines.

Relatedly, EPA states:

> 5) Consider and incorporate applicable engineering controls and/or personal protective equipment into exposure scenarios.
>
> EPA will review potential data sources on engineering controls and personal protective equipment as identified in Table Apx B-6 in Appendix B and determine their applicability and incorporation into exposure scenarios during risk evaluation. (p. 66)

EPA provides no indication as to how it will "consider and incorporate" such controls or equipment into its exposure scenarios. Myriad questions arise. What assumptions will be made as to their extent of use, their efficacy, etc.? Limitations on the extent of use and the efficacy of workplace controls, especially for PPE, have been illuminated by both OSHA and EPA. EDF discusses these concerns at length in section 13 of these comments.

EPA's vague and unexplained statements about its planned analyses raise serious concerns and often lack any empirical basis. EPA must analyze occupational exposures based on the best available science, and EPA must use its information authorities to obtain reasonably available information about these exposures.

C. EPA over-relies on limited and incomplete TRI data to exclude or dismiss the significance of numerous exposure pathways.

EPA makes extensive use of the very limited 2016 data on 1-BP reported under the Toxics Release Inventory (TRI). It should be noted that 1-BP was only recently added to the TRI and 2016 was the first year it was required to be reported. That may help explain why a TRI report for 1-BP was received from only about 40% of facilities (55 of 140 facilities) expected to report the chemical, a fact EPA discusses (p. 32) but then largely ignores when citing TRI data as the basis for excluding exposure pathways or asserting low release or exposure to 1-BP. In fact, the gap between reported and actual releases may be even worse than that: EPA's summary of TRI data in Table 2-6 on page 33 of the problem formulation shows that very few facilities (often only one) reported any releases at all to various media or waste management facilities, suggesting that there may be more facilities that did not report.

EPA's decision to make sweeping exclusions of exposure pathways or assume negligible releases and exposures based on TRI data alone is troubling, given EPA's own speculation as to why such a large gap exists between the number of TRI reports it received vs. what was expected:

> The difference in estimated versus actual reporting facilities could be due to several factors such as, 1) facilities could be moving away from using 1-BP; 2) *some facilities may not yet be aware of the reporting requirements since this is the first year of*

> *reporting*; 3) *facilities could be below the threshold for reporting.* Facilities are required to report if they manufacture (including import) or process more than 25,000 pounds of 1-BP, or if they otherwise use more than 10,000 pounds of 1-BP. (pp. 32-3, emphasis added)

Beyond this paragraph, EPA never grapples with the enormous uncertainty and likely unreliability of the TRI data on which it so heavily relies, which is further explored below.

Exclusion of exposures from disposal pathways: EPA relies heavily on 2016 TRI data to justify its exclusion of disposal pathways from the 1-BP risk evaluation. For example, EPA states:

> Table 2-6 shows TRI reports approximately 58,000 pounds of disposal to *a single RCRA Subtitle C landfill.* EPA will not further analyze releases to hazardous waste landfills because these types of landfill mitigate exposure to the wastes. TRI also reports approximately 90,000 pounds of 1-BP transferred to other off-site landfills [3 in total]. Further review of TRI data indicated that all reported transfers "other off-site landfills" were to facilities permitted to manage RCRA regulated waste. (p. 34, emphasis added)

EPA has not provided to the public its "further review of TRI data." Given the inadequacy of the TRI data the agency is relying upon, it is certainly plausible that significantly more 1-BP is transferred to "other off-site landfills," which may not be subject to RCRA subtitle C requirements. As discussed above, 1-BP is not listed as a hazardous waste under RCRA.

Assumed low releases to surface water and low exposures via drinking water: EPA reports that there are no water monitoring data for 1-BP (p. 34). Despite their limitations, EPA relies nearly exclusively on TRI data to argue that it need not further analyze exposures via surface water and effectively can conclude such exposures are safe.

First, EPA appears to accept without question the reliability of TRI water release data, even though "[i]n the 2016 TRI, only 1 facility out of 55 reported releases to water." (p. 34) EPA uses the data from this one facility to conclude that this particular discharge was safe: "This facility reported 5 lbs of direct surface water discharge; assuming the release occurred over a single day, the surface water concentration in reported receiving waters is well below the COC [concentration of concern] based on EPA's preliminary calculations." (p. 34)

Then EPA uses those single-facility data to model surface water concentrations *in general*: "EPA used the reported releases from EPA's Toxics Release Inventory (TRI) to predict surface water concentrations near reported facilities for this Problem Formulation." (p. 35) EPA then definitively concludes, based on the TRI data from this one facility, that "*releases to water are very low*." (p. 35, emphasis added)

Building from there, EPA uses an analysis based on the limited TRI data, without any qualification, to assert *all drinking water* exposures are also low:

> Recent TRI reporting indicated 0 pounds released to POTWs and 5 pounds released directly to water in 2016. EPA pretreatment regulations for industrial users discharging

> wastewater to POTWs *are expected* to limit the discharge of 1-BP to POTWs and ultimately to surface water (see Section 2.3.4). Waste disposal practices and 1-BP's rapid volatilization from water *are expected* to mitigate drinking water exposure potential and there is no data of 1-BP found in US drinking water." (p. 39, emphases added)

EPA's reliance on extremely limited TRI data, coupled with unsupported "expectations" that discharges and exposures will be minimal, is capped off here with an outlandish assumption that the lack of monitoring data for 1-BP means it must not be present. Has the chemical even been looked for in drinking water? No data on that question are cited by EPA. And elsewhere EPA notes:

> Environmental monitoring data were not identified in the 2016 Draft Risk Assessment (U.S. EPA, 2016b); however, any environmental monitoring data that may result from the updated literature search will be considered. (p. 34)

EPA cannot equate a lack of evidence of 1-BP's presence in water with evidence of its absence, but that is precisely what EPA appears to be doing here.

The last step in EPA's construction of its house of cards comes on page 68:

> Environmental hazards will not be further analyzed *because exposure analysis* conducted using physical and chemical properties, fate information and *TRI environmental releases for 1-BP* show that ecological receptors are not significantly exposed to TSCA-related environmental releases of this chemical.

EPA makes a wholly exposure-based argument for its decision not to even consider the environmental hazards the chemical may present via water exposures, an approach industry interests have long advocated for, but one which fails to constitute sound science. (Later in these comments, in Section II, EDF addresses additional problems with EPA's calculations of its concentrations of concern for aquatic species.)

Rather than constructing such a tenuous line of argument to compensate for the lack of any water monitoring data for 1-BP, EPA should use its clear TSCA authority under section 4 to require the development of the data.

More broadly, EPA cannot justify its heavy reliance on TRI data without resolving the discrepancies discussed earlier that cast serious doubt on the completeness and accuracy of these data.

D. EPA has excluded without justification identified hazards of 1-BP from its quantitative risk characterization.

EPA states:

> For the 2016 Draft Risk Assessment (U.S. EPA, 2016b) on 1-BP, EPA evaluated studies for the following non-cancer hazards: acute toxicity (acute lethality at high concentrations

only), blood toxicity, immunotoxicity, cardiovascular toxicity, liver toxicity, kidney toxicity, reproductive toxicity, developmental toxicity, and neurotoxicity. A comprehensive summary of all endpoints considered can be found in the 2016 Draft Risk Assessment. *Five health hazards were used for quantitative risk characterization* and will be evaluated using our systematic review approach. (p. 43, emphasis added)

EPA provides no explanation or justification as to why and how these five, the last five in the list of "-icities" in the above excerpt, were selected. Nor has it explained why it has excluded from the quantitative risk characterization acute toxicity (acute lethality at high concentrations only), blood toxicity, immunotoxicity, and cardiovascular toxicity that were identified in the 2016 draft risk assessment for 1-BP. It needs to do so. Absent a compelling justification supported by the best available science and reasonably available information, EPA must analyze these hazards as well when developing its quantitative risk characterization.

E. EPA has not identified all relevant potentially exposed or susceptible subpopulations.

At the end of its section on Human Health Hazards (section 2.4.2.3), EPA states:

> In developing the hazard assessment, EPA will evaluate available data *to ascertain whether* some human receptor groups may have greater susceptibility than the general population to the chemical's hazard(s). (p. 45, emphasis added)

This statement stands in contrast to the analogous subsection under Human Exposure (p. 40, section 2.3.5.4), where EPA identified specific subpopulations that "EPA expects to consider in the risk evaluation due to their greater exposure." TSCA requires that EPA identify "potentially exposed or susceptible subpopulations" (TSCA section 6(b)(4)(D)), including those that "due to ... greater *susceptibility* ... may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture." TSCA section 3(12).

Given the evidence of reproductive and developmental toxicity for 1-BP, it is clear that, at a minimum, adults of childbearing age, pregnant women, infants and children should be explicitly identified as such subpopulations. Other subpopulations may also warrant identification based on the available hazard data. Yet, unlike in the exposure section (p. 40), EPA has not identified *any* vulnerable populations based on greater susceptibility. This needs to be remedied.

23. EPA relies extensively on assumptions that are inconsistent or not supported with data, and on models that are not conservative, despite claims to the contrary.

Terrestrial environmental exposures: EPA states:

> *EPA does not plan to further analyze terrestrial exposures*, due to low expected toxicity (see Section 2.4.1) and low expected exposure based on the physical/chemical properties (e.g., high vapor pressure; see Section 2.1). (p. 35, emphases added)

Yet the cited section 2.4.1 provides no data that demonstrate low toxicity; rather, it cites an *absence* of toxicity data – a clear data gap EPA fails to identify or indicate whether or how it will address:

> During data screening, there were no available sediment, soil, nor avian toxicity studies found in the scientific literature for 1-BP. The toxicity of 1-BP is expected to be low *based on the lack of on-topic environmental hazard data for 1-BP to sediment and terrestrial organisms in the published literature* and the physical/chemical/fate properties (relatively high volatility (Henry's Law constant of 7.3X10-3 atm-m3/mole), high water solubility (2.4 g/L), and low log Koc (1.6) suggesting that 1-BP will only be present at low concentrations in these environmental compartments. (p. 41)

The physical/chemical/fate properties EPA cites may be germane to some sediment- or soil-dwelling organisms, but in no way rule out exposure of terrestrial organisms through inhalation – a pathway that EPA elsewhere acknowledges is quite relevant to the subset of terrestrial organisms otherwise known as humans. Moreover, EPA's effort to dismiss toxicity data gaps based on exposure arguments does not reflect sound science. Nor does EPA's equating a lack of on-topic hazard data with evidence of low toxicity.

EPA must use its information authorities to generate hazard data for sediment-dwelling and other terrestrial organisms.

Dermal exposures: With respect to occupational exposures, EPA states:

> [D]ermal exposure to 1-BP based on a single finite exposure event is likely negligible. *** EPA also expects the dermal absorbed fraction to be low (0.16 percent – see discussion under Dermal section of Section 2.3.5.2). However, there is potential for increased dermal penetration for uses where occluded exposure, repeated contact, or dermal immersion may occur. (pp. 36-7)

The first part of the discussion seeks to dismiss dermal exposure as insignificant based on an assumption of a single exposure event involving direct contact with skin that is also exposed to the air. But it is the second set of scenarios, which EPA treats as *exceptions*, that are far more likely to characterize occupational exposures: e.g., repeated contact, liquid or vapor trapped against skin by gloves.

In discussing consumer exposures, EPA states:

> Dermal exposure may occur via vapor/mist deposition onto skin or via direct liquid contact during use, particularly in occluded scenarios. (p. 38)

This scenario is equally or more likely to apply in occupational settings, yet is not mentioned in that section of the problem formulation (section 2.3.5.1).

Still discussing consumer exposures, EPA goes on to state:

> However, measurements of skin penetration were one to two orders or magnitude higher in occluded environments where evaporation losses were not considered (transient 10 minute exposures, or 'infinite' 3 hour exposures). Based on this information, dermal exposure in non-occluded scenarios will be a less significant route of exposure when compared to occluded scenarios, however there may be *exceptions* such as situations of transient or infinite exposures (e.g., vapor trapped against skin by gloves or continued contact with a wet rag) or where there is greater potential for dermal penetration due to longer durations of exposure. (pp. 38-9)

This extent of discussion and reference to data for occluded situations, characterized as "exceptions," are only included in the consumer section, and not provided in the occupational section on dermal exposures where they are especially likely to occur.

Later, in discussing the conceptual model for consumer activities, EPA states:

> Some products may be purchased and used as a liquid. For these uses, consumers may have dermal contact from occluded exposures such as holding a rag soaked in liquid 1-BP where limited evaporation rates and penetration may be expected to be higher in these scenarios. *EPA does not expect to further analyze dermal exposure to 1-BP vapor*, however EPA does expect to further analyze direct dermal contact with liquid 1-BP for consumers during the risk evaluation phase. (p. 49)

Yet just pages earlier (and cited just above), EPA had acknowledged the potential significance of dermal exposures to *vapor*, referring to "vapor trapped against skin by gloves or continued contact with a wet rag) or where there is greater potential for dermal penetration due to longer durations of exposure." (pp. 38-9) Why is EPA now stating it will ignore such exposures altogether?

EPA's apparent decision to exclude certain dermal exposures to 1-BP altogether, or to conclude with no further analysis that certain dermal exposures are negligible, is inconsistent with TSCA's mandate that EPA consider the combination of exposures to a chemical in assessing its risks, a requirement discussed earlier in these comments (see Section 1.A.ii). It is also not consistent with EPA's own problem formulation, where EPA states:

> Based on the physical-chemical properties and high evaporative losses compared to dermal absorption as described in Section 2.3.5.2, non-occluded dermal exposures are not expected to be the primary route of exposure for consumers, *although dermal exposures will contribute to the overall exposure*. (p. 49, emphasis added)

This logic on the need to look at all contributors to overall exposure applies to numerous pathway scenarios that EPA says it will not further analyze because inhalation is deemed the "major" exposure pathway. As discussed earlier in these comments (see Section 1.A.ii), TSCA includes nothing that allows EPA to limit itself only to assessing the "major source" of exposure to 1-BP or other chemicals. EPA must analyze dermal exposures to 1-BP, including how these exposures contribute to overall exposure.

Ingestion: EPA states:

> EPA does not plan to further analyze exposure to consumers via ingestion of 1-BP. Ingestion is not expected to be a primary route of exposure. Based on the vapor pressure, 1-BP will exist as a vapor/mist during use. (p. 38)

Yet as just noted, EPA acknowledges elsewhere that "[s]ome products may be purchased and used as a liquid." (p. 49) How can EPA wholly rule out ingestion, including by accident?

Modeling of surface water concentrations: EPA asserts that its assumption that wastewater treatment removal is 0% is conservative. However, this is not the case. EPA itself notes that "reported releases likely already account for wastewater treatment, which means any removal has already been accounted for." (p. 35) It, therefore, is a reasonable (but not necessarily conservative) assumption.

EPA also asserts that its concentrations of concern (COCs) for aquatic effects are "conservative."

Discussing its acute COC:

> The acute COC of 4,860 µg/L, derived from experimental fish endpoint, is used as a *conservative* hazard level in this problem formulation for 1-BP. (p. 42, emphasis added)

Discussing its chronic COC:

> The chronic COC of 243 µg/L, derived from experimental fish endpoint, is used as the *lower bound* hazard level in this problem formulation for 1-BP. (p. 43, emphasis added)

EPA implies that its calculations of COCs are conservative at least in part because of its use of assessments factors. The use of such factors is not conservative: They account for *real-world sources of variability as well as database limitations*, and cannot be construed as "safety factors" that yield conservative estimates.[113] As EPA states:

> The application of assessment factors is based on established EPA/OPPT methods (U.S. EPA, 2013b, 2012c) and were used in this Problem Formulation to calculate lower bound effect levels (referred to as the concentration of concern; COC) that would likely encompass more sensitive species not specifically represented by the available experimental data. Also, assessment factors are included in the COC calculation to account for differences in inter- and intra-species variability, as well as laboratory-to-field variability. (p. 42)

Notably, EPA's derivation of its chronic COC is based on no actual chronic toxicity data. EPA states:

> Since there are *no long-term chronic studies for 1-BP*, the fish 96-hr LC50 of 24.3 mg/L (the lowest acute value in the dataset) is divided by an acute-to-chronic ratio (ACR) of 10 to obtain a chronic value (ChV) for fish. (p. 43)

[113] *See* Section 14 of these comments.

EPA should have identified this as a data gap and taken steps to address it. EPA provides no justification for its application of an "acute-to-chronic ratio" or its specific value of 10, nor does it provide even a citation to the use of such values in other contexts. Even a cursory search of the literature indicates that an ACR of at least 100 may be needed to be sufficiently protective.[114]

24. EPA's problem formulation reveals numerous data gaps, yet EPA provides no indication it intends to address any of them.

As discussed at length earlier in these comments (Section 8), EPA's assertion that it will not and need not use the enhanced authorities Congress gave it in reforming TSCA in 2016 to address information needs in conducting risk evaluations is deeply troubling. In this section we provide a list of examples of the many data gaps that plague the 1-BP risk evaluation and EPA's resort to insufficient approaches to work around the gaps without actually filling them.

1. EPA appears adamant on relying on models rather than requiring the development of information to fill gaps or resolve discrepancies and uncertainties in the available data – even where the models contribute to that uncertainty based on variable results. For example, EPA states:

> The EPI Suite™ module that predicts biodegradation rates ("BIOWIN" module) was run using default settings to estimate biodegradation rates of 1-BP under aerobic conditions. Three of the models built into the BIOWIN module (BIOWIN 2, 5 and 6) estimate that 1-BP will not rapidly biodegrade in aerobic environments, while a fourth (BIOWIN 1) estimates that 1-BP will rapidly biodegrade in aerobic environments. These results support the biodegradation data presented in the 1-BP Scope Document (EPA-HQ-OPPT-2016-0741-0049), which demonstrate a range of biodegradation rates under aerobic conditions. The model that estimates anaerobic biodegradation (BIOWIN 7) predicts that 1-BP will rapidly biodegrade under anaerobic conditions. Further, previous

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[114] *See* Martin May, et al., *Evaluation of acute-to-chronic ratios of fish and Daphnia to predict acceptable no-effect levels*, 28:1 ENVTL. SCIENCES EUROPE 16 (2016), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5044967/; Jan Ahlers, et al., *Acute to chronic ratios in aquatic toxicity - Variation across trophic levels and relationship with chemical structure*, 25:11 ENVTL. TOXICOLOGY & CHEMISTRY (Dec. 2009), 10.1897/05-701R.1. ("For fish, daphnids, and algae, acute to chronic ratios (ACRs) have been determined from experimental data regarding new and existing chemicals. Only test results in accord with the European Union Technical Guidance Document (TGD) and validated by authorities were considered. Whereas the median ACRs of 10.5 (fish), 7.0 (daphnids), and 5.4 (algae) are well below the ACR safety factor of 100 as implied by the TGD, *individual ACRs vary considerably and go up to 4400. The results suggest that a safety factor of 100 is not protective for all chemicals and trophic levels.* Neither a correlation between ACR and baseline toxicity as modeled through the logarithmic octanol-water partition coefficient nor an ACR correlation across trophic levels exists. Narcosis is associated with a preference for a low ACR; nevertheless, low ACRs are frequently obtained for nonnarcotics. Analysis of chemical structures led to the derivation of structural alerts to identify compounds with a significantly increased potential for a high ACR, which may prove to be useful in setting test priorities. *At present, however, life-cycle tests are the only way to conservatively predict long-term toxicity.*") (emphases added).

assessments of 1-BP found that biodegradation occurred over a range of rates from slow to rapid [Toxicological Profile for 1-Bromopropane; (ATSDR, 2017)]. (p. 30)

2. EPA states: "*No measured bioconcentration studies for 1-BP are available*. An estimated BCF of 11 and an estimated BAF of 12 suggest that bioconcentration and bioaccumulation potential in aquatic organisms is low (BCF and BAF <1,000)." (p. 31)

Rather than require such bioconcentration studies be performed, EPA relies on models without any characterization of the resulting uncertainty associated with the conclusions it draws. Yet existing models have often been criticized as unreliable and often under-predictive of bioconcentration and bioaccumulation potential.[115]

3. EPA states: "Currently, EPA is not aware of the presence of 1-BP in recycled articles." (p. 34) This clear data gap is used by EPA to suggest that exposures from recycling activities are not of concern. In reality, it simply means the question cannot be answered without addressing the data gap.

4. EPA states: "[T]here were no available sediment, soil, nor avian toxicity studies found in the scientific literature for 1-BP. The toxicity of 1-BP is expected to be low based on the lack of on-topic environmental hazard data for 1-BP to sediment and terrestrial organisms in the published literature and the physical/chemical/fate properties (relatively high volatility (Henry's Law constant of 7.3X10-3 atm-m3/mole), high water solubility (2.4 g/L), and low log Koc (1.6) suggesting that 1-BP will only be present at low concentrations in these environmental compartments." (p. 41)

Astoundingly, EPA here relies on the lack of available data to conclude toxicity must be low.

5. EPA states: "For most high-priority chemical substances level(s) can be characterized through a combination of available monitoring data and modeling approaches." (p. 57)

EPA simply asserts this as fact, even as it seeks (as noted on this same page) more of the very same data. And for 1-BP, EPA has acknowledged there are no monitoring data available (p. 34).

6. EPA states: "Additionally, for conditions of use where no measured data on releases are available, EPA may use a variety of methods including the application of *default assumptions.* *** EPA will also review data sources containing estimated data and *identify data gaps*." (p. 58)

While defaults have their place, there is no excuse for EPA failing to even mention its authority to require the development and submission of the information it needs. And to date, EPA has done little to nothing to identify data gaps, and instead actively seeks to avoid doing so.

7. EPA states: "If measured values resulting from sufficiently high-quality studies are not available (to be determined through the systematic review process), chemical properties will be estimated using EPI

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[115] *See, e.g.*, Arnot, J.A. & Frank Gobas, *A review of bioconcentration factor (BCF) and bioaccumulation factor (BAF) assessments for organic chemicals in aquatic organisms*, 14 ENVIRON. REV. 257-297 (2006), http://rem-main.rem.sfu.ca/papers/gobas/A%20Review%20of%20Bioconcentration%20factor%20(BCF)%20and.pdf

Suite, SPARC, and other chemical parameter estimation models. Estimated fate properties will be reviewed for applicability and quality." (p. 60)

Again EPA skips right over any mention of mandating data development or submission.

8. EPA states: "EPA will review *reasonably available* data that may be used in developing, adapting or applying exposure models." (p. 61, emphasis added)

In its final risk evaluation rule, EPA defines "reasonably available" as information that EPA "possesses *or can reasonably generate, obtain*, and synthesize for use in risk evaluations, considering the deadlines specified in TSCA section 6(b)(4)(G) for completing such evaluation." 40 CFR § 702.33, emphasis added. Yet, in the problem formulation, EPA makes no mention of efforts to use its authorities to generate or obtain needed information.

9. EPA states: "For some OSHA data, NAICS codes included with the data will be matched with potentially applicable conditions of use, and *data gaps will be identified where no data are found for particular conditions of use. EPA will attempt to address data gaps identified as described in steps 2 and 3 below*." (p. 64, emphasis added)

Step 2 entails the use of data on surrogate chemicals. Step 3 entails the use of models. No step is indicated that would entail requiring submission or development of the needed data.

10. EPA states: "Review reasonably available exposure data for surrogate chemicals that have *uses and chemical and physical properties similar to 1-BP*. *** For several uses including use of adhesives, and cleaning products, EPA believes that trichloroethylene and other similar solvents may share the same or similar conditions of use and may be considered as surrogates for 1-BP." (p. 64, emphasis added)

EPA makes no mention of the need for surrogate chemicals to have similar environmental and biological fate as well as chemical and physical properties. Nor does it appear to be planning to compare the chemicals on the basis of any available toxicity information. While EDF does not oppose including surrogate data when relevant, it should not be the option of first resort and be used to excuse EPA from actively pursuing such data through its information authorities.

11. EPA states: "*If sufficient dermal toxicity studies are not identified* in the literature search to assess risks from dermal exposures, then a *route-to-route extrapolation* from the inhalation and oral toxicity studies would be needed to assess systemic risks from dermal exposures." (p. 70, emphasis added)

Again, EPA makes no mention of filling the data gap.

EPA should use its information authorities to fill the above data gaps in order to develop a risk evaluation consistent with the best available science and reasonably available information.

25. EPA's apparent effort to cast doubt on the carcinogenic potential of 1-BP is without merit.

EPA states:

> The exact mechanism/mode of action of 1-BP carcinogenesis is not clearly understood, however, *the weight-of-evidence analysis for the cancer endpoint is inconclusive* but does not rule out a probable mutagenic mode of action for 1-BP carcinogenesis. In the 2016 Draft Risk Assessment (U.S. EPA, 2016b), EPA derived an inhalation unit risk (IUR) based on lung tumors in female mice. This health hazard was used for quantitative risk characterization and will be evaluated using our systematic review approach. (p. 45, emphasis added)

EPA's assertion that "the weight-of-evidence analysis for the cancer endpoint is inconclusive" is not supported with any citations or even discussion. It is not clear whether the "inconclusive" claim is intended to apply only to mechanism/mode of action or more broadly to 1-BP's carcinogenicity. In either case, it is not consistent with the conclusions of several authoritative bodies, including EPA:

- The National Toxicology Program's (NTP) *Report on Carcinogens* concluded in 2013 that 1-BP is "reasonably anticipated to be a human carcinogen."[116]
- The Agency for Toxic Substances and Disease Registry (ATSDR) confirmed this classification in its 2017 profile:

  > The potential carcinogenicity of 1-bromopropane has been examined in bioassays in rats and mice (Morgan et al. 2011; NTP 2011). In both bioassays, animals were exposed 6 hours/day, 5 days/week for up to 105 weeks. Rats were exposed to 0, 125, 250, or 500 ppm 1-bromopropane vapors, while mice were exposed to 0, 62.5, 125, 250, or 500 ppm 1-bromopropane vapors. 1-Bromopropane was a multisite carcinogen in rats, significantly increasing the incidence of large intestine adenomas in females (500 ppm), skin keratoacanthoma in males (≥250 ppm), skin keratoacanthoma, basal cell adenoma, or squamous cell carcinoma in males (≥125 ppm), malignant mesothelioma in males (500 ppm), and pancreatic islet adenoma in males (≥125 ppm). In mice, exposure to 1-bromopropane significantly increased the incidence of combined alveolar/bronchiolar adenoma or carcinoma in females (≥62.5 ppm).[117]

- EPA's own 2016 draft risk assessment for 1-BP, based on a weight-of-evidence analysis, concluded:

  > Following EPA's Guidelines for Carcinogen Risk Assessment, *overall, the totality of the available data/information and the weight of evidence* support a

[116] Natl'l Toxicology Program, *Report on carcinogens Monograph for 1-bromopropane* at 49 (Sept. 2013), https://ntp.niehs.nih.gov/ntp/roc/thirteenth/monographs_final/1bromopropane_508.pdf.
[117] Agency for Toxic Substances & Disease Registry, *Toxicological profile for 1-bromopropane* at pp. 77-8 (Aug. 2017), https://www.atsdr.cdc.gov/ToxProfiles/tp209.pdf.

> justifiable basis to conclude a probable mutagenic mode of action for 1-BP carcinogenesis. 1-BP may be considered to be "*Likely to be Carcinogenic in Human* [sic]".[118]

Regarding EPA's effort in the above excerpt from the problem formulation to cast doubt on 1-BP's carcinogenic potential by stating "The exact mechanism/mode of action of 1-BP carcinogenesis is not clearly understood," EDF has addressed this tenuous argument earlier in these comments (see section 17), noting that the biological processes underlying observed effects are often not well understood but that serves as no basis to reject the actuality of the effects.

26. EPA's problem formulation contains several statements relating to confidential business information (CBI) that are or may be inconsistent with its authorities and obligations under TSCA.

1. EPA states: "Based on market information from other sources, EPA expects degreasing and spray adhesive to be the primary uses of 1-BP; however, the *exact use volumes associated with these categories are claimed CBI* in the 2016 CDR (U.S. EPA, 2016a)." (p. 27, emphasis added)

EPA's failure to conduct the timely reviews TSCA mandates of CBI claims made in submissions under the CDR – which were collected two years ago – is resulting in the public being precluded from understanding the extent of consumer uses of this chemical.

2. EPA states: The derived acute COC (4,860 ppb) and chronic COC (243 ppb) are based on environmental toxicity endpoint values (e.g., LC50) from ECHA. *Full study reports associated with these COCs were not available and will not be available in the future*." (p. 43, emphasis added)

It is not acceptable for EPA to rely only on summaries of studies without access to the full study. Nor is it appropriate for EPA to deny the public access to such studies, which clearly constitute health and safety studies under TSCA and are not eligible for CBI protection. EPA could readily require the submission of the full studies under TSCA, using its section 8 or 11(c) authority.

3. EPA states: "EPA may consider any relevant confidential business information (CBI) in the risk evaluation in a manner that protects the confidentiality of the information from public disclosure." (p. 57)

This statement ignores the major changes made to the CBI provisions of TSCA section 14. Companies must substantiate most claims for CBI protection and EPA must review many of them within 90 days of submission of the information. Any claim that does not meet all applicable requirements cannot be protected from disclosure.

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[118] U.S. EPA, *TSCA work plan chemical risk assessment: Peer review draft 1-bromopropane: (n-Propyl bromide) Spray Adhesives, Dry Cleaning, and Degreasing Uses CASRN: 106-94-5* at 95 (2016), https://www.epa.gov/sites/production/files/2016-03/documents/1-bp_report_and_appendices_final.pdf (first emphasis added).

Further, EPA fails to acknowledge that health and safety studies are expressly not eligible for protection as CBI under TSCA, subject only to two very narrow exceptions; see section 14(b)(2). All such information not subject to the exceptions needs to be made public.

27. Comment in response to a comment letter from Albemarle on the 1-BP problem formulation.

A comment letter was posted in the docket for this problem formulation on July 26, 2018, from Charles R. Nestrud, Attorney, Barber Law Firm on behalf of Albemarle Corporation.[119]

The comment letter makes numerous assertions that some of the information EPA provides in the problem formulation is incorrect or outdated. In doing so, the commenter repeatedly refers to information that Albemarle or others have provided to EPA, that "is now available," or that "is attached." Yet no attachments are included with the letter, and our review of the docket has not located any of the claimed information. Nor can we find them in the bibliography for the problem formulation.

The letter makes reference to multiple unpublished toxicity studies, none of which are attached to the letter or in the docket even though the letter states that "EPA has the report." The letter also refers to "six peer-reviewed manuscripts" that "have been provided to EPA." Specific citations were not provided and it does not appear that any of these manuscripts are in the docket.

EPA promptly needs to provide public access to all of the information referred to in this letter if it intends to rely on it in conducting the risk evaluation of 1-BP. Below is a list of the information referred to in the letter:

(1) ICL Big Blue MutaMouse study
(2) Enviro Tech International Big Blue MutaMouse study
(3) Albemarle's "duplicate negative" Ames test
(4) 6 peer reviewed manuscripts of entire NTP database of 2-year studies
(5) Trinity facility exposure assessment ("attached")
(6) Albemarle's usage and exposure assessment ("attached")
(7) Enviro Tech International usage and exposure scenarios

The letter also refers to additional information Albemarle intends to provide EPA "as it becomes available" or that will arise through additional work that Albemarle or Enviro Tech wishes to work with EPA to develop. EPA needs to commit to making this publicly available promptly upon its receipt or development by EPA.

[119] *See* https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0010.

Comments on Carbon Tetrachloride

28. EPA has excluded or failed to sufficiently analyze numerous conditions of use and exposure pathways for carbon tetrachloride.

A. EPA's exclusion of numerous exposure pathways based on other environmental statutes fails to address the ongoing exposures posed by these pathways.

As with the problem formulations for most of the other nine chemicals, EPA has proposed to exclude a number of exposure pathways on the basis of other statutes administered by EPA. *See* U.S. EPA, Problem Formulation of the Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-) CASRN: 56-23-5 at pp. 48-9 (May 2018), https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0733-0068. This approach is illegal and arbitrary and capricious for the reasons articulated above in Section 5. The evidence before the agency thoroughly establishes that exposures still occur through these pathways, and EPA should analyze these pathways to produce a risk evaluation consistent with reasonably available information and best available science.

Clean Air Act: First, EPA has stated that it does not expect to include emission pathways to air from commercial and industrial stationary sources or associated inhalation exposure of the general population or terrestrial species, because carbon tetrachloride is a hazardous air pollutant (HAP). (p. 48) EPA states that the emissions from stationary sources of carbon tetrachloride have been adequately addressed because there are technology-based standards applicable to certain releases of the chemical to ambient air, yet those regulations do not cover all releases of carbon tetrachloride to the air. For instance, the National Emissions Inventory (NEI) data from 2014 identifies 28 different sectors that released carbon tetrachloride to the air. These emission sources include, but are not limited to, chemical manufacturing, pulp and paper processing, waste disposal, oil and gas production, and fuel combustion.[120] While EPA has promulgated regulations under the Clean Air Act (CAA) for carbon tetrachloride in some chemical manufacturing areas and for plywood and composite wood products, the CAA regulations for carbon tetrachloride listed in the Appendix do not address other sources of carbon tetrachloride identified in the NEI. Additionally, for sources that are covered by the CAA regulations, the NEI indicates that those sources continue to emit carbon tetrachloride to the air (e.g., chemical manufacturing resulted in 89,839 pounds of carbon tetrachloride air emissions in 2014).

Safe Drinking Water Act: EPA will also exclude drinking water as an exposure pathway because EPA has set a Maximum Contaminant Level (MCL) "as close as feasible to a health-based" non-enforceable Maximum Contaminant Goal Level (MCLG) under the Safe Drinking Water Act. Whether a standard is "feasible" refers to the ability to monitor water quality and to treat the water, both of which are notably "nonrisk factors" that EPA is not allowed to consider in risk evaluations under TSCA. *See* 15 U.S.C. § 2605(b)(4)(A). Additionally, the MCLG is the level in drinking water at which "no known or anticipated adverse effect on the health of persons would occur." 40 C.F.R. § 141.2. If anything, this standard

[120] *See* 2014 NATIONAL EMISSIONS INVENTORY (NEI) DATA, https://www.epa.gov/air-emissions-inventories/2014-national-emissions-inventory-nei-data (last visited Aug. 2, 2018) (the data for carbon tetrachloride is included in the supplement at the end of the carbon tetrachloride comment).

(which is zero for carbon tetrachloride) is much closer to the solely risk-based standard required for risk evaluations under TSCA, yet it is not the standard by which EPA regulates drinking water.

EPA's own data indicate that this "feasibility" standard results in continuing exposures to carbon tetrachloride in drinking water. For instance, based on 2015 data cited by EPA 6% of modeled drinking water exposures were above the MCL. (p. 38) Yet in the problem formulation EPA has decided it will exclude those exposures as having been "adequately assessed" and it will assume they present zero risk. These data do not support a conclusion that carbon tetrachloride in drinking water poses no risk.

Additionally, EPA indicated that the USGS has detected carbon tetrachloride in community water systems and that the data are available through a portal. (p. 35) The problem formulation does not identify the communities, nor does it indicate whether EPA has checked the USGS database. After a rudimentary search for carbon tetrachloride in that database, EDF found that over 44,000 sites had sampling data where carbon tetrachloride was present.[121] At a minimum, EPA must address these data more comprehensively than merely stating they exist. EPA must analyze these actual exposures in its risk evaluation.

Clean Water Act: EPA also plans to exclude exposures to carbon tetrachloride through ambient water pathways. According to EPA this pathway has been addressed for human health because there is a recommended water quality criterion for carbon tetrachloride for human health under section 304(a) of the Clean Water Act (CWA). However, elsewhere in the problem formulation EPA estimate that 8% of carbon tetrachloride in wastewater remains in effluent discharged after treatment. (p. 30) EPA does not address the exposure potential of this effluent in ambient water, and instead will simply ignore such exposures.

Biosolids will also not be evaluated because EPA says its Office of Water is developing modeling tools in order to conduct risk assessments. (p. 49) While such activity is no doubt useful and may eventually lead to an actual assessment of risk and needed controls, those latter activities are speculative at this point and provide no basis for excluding such exposures from this risk evaluation. See our earlier comments in Section 5.E.

Resource Conservation and Recovery Act: In regards to disposal, EPA states it will not evaluate any pathways. Yet it has failed to provide any analysis to demonstrate the extent to which existing regulations actually eliminate associated exposures. For example, EPA states only that migration to groundwater from RCRA subtitle C landfills is "likely" to be mitigated by landfill design. (p. 33)

EPA has provided no data or analysis demonstrating that disposal of hazardous or solid wastes, even if compliant with RCRA, pose no risk to the general population, vulnerable subpopulations, terrestrial species or other receptors.

[121] WATER QUALITY DATA, https://www.waterqualitydata.us/portal/#characteristicName=Carbon%20tetrachloride&mimeType=csv&sorted=no (last visited Jul. 18, 2018).

In sum, EPA should analyze the excluded pathways and assess the real-world exposures occurring through these pathways.

B. EPA has inappropriately excluded a number of conditions of use based on an unsubstantiated theory that exposures will be "de minimis."

EPA plans to exclude the industrial, commercial, and consumer uses of carbon tetrachloride in commercially available aerosol and non-aerosol adhesives, paints/coatings, and cleaning/degreasing solvent products because it asserts these uses will result in de minimis exposures. (pp. 20-21) This assertion bears greater scrutiny.

EPA states that domestic production and importation of carbon tetrachloride "is currently prohibited under regulations implementing the Montreal Protocol" and the Clean Air Act, but notes that this prohibition excludes carbon tetrachloride when it is transformed, destroyed, or used for "essential laboratory and analytical uses." (p. 20)

EPA also states that the Consumer Product Safety Commission (CPSC) has banned the use of carbon tetrachloride in household products since 1970, but notes there are exceptions for "unavoidable manufacturing residues *** that under reasonably foreseen conditions of use do not result in an atmospheric concentration of carbon tetrachloride greater than 10 parts per million." (p. 20)

EPA goes on to note that the regulations implementing the Montreal Protocol and the Clean Air Act provide for "a limited number of specific manufacturing uses of carbon tetrachloride as a process agent (non-feedstock use) in which carbon tetrachloride may not be destroyed in the production process" and that "carbon tetrachloride is used in the manufacturing of other chlorinated compounds that may be subsequently added to commercially available products (i.e., solvents for cleaning/degreasing, adhesives/sealants, and paints/coatings)." (p. 20) While "EPA expects insignificant or unmeasurable concentrations of carbon tetrachloride in the manufactured chlorinated substances in the commercially available products," the only corroborating sources it provides are qualified comments, backed with no actual data, from representatives of the chemical industry asserting that the levels are low.

While the regulatory exclusions in this setting – regulation of carbon tetrachloride due to its stratospheric ozone depletion potential – may be reasonable, it is entirely unclear from the problem formulation how often the regulatory exceptions are relied on, what levels of release and exposure result, and what risks to human health or the environment these exposures pose.

In fact, releases of carbon tetrachloride to the air remain a concern to the parties to the Montreal Protocol. In 2015 (and in 2011), the parties to the Montreal Protocol released a decision requesting an investigation into the discrepancies between the levels of carbon

tetrachloride observed in the atmosphere versus reported data.[122] The decision notes with concern that

> derived emissions of carbon tetrachloride, based on its estimated lifetime and its accurately measured atmospheric abundances, have become much larger over the last decade than those from reported production and usage.[123]

The reasons given for wholly excluding these uses from EPA's risk evaluation have no basis in the law, or even in EPA's rationale for excluding uses that are "adequately addressed" by other statutes. The different purposes underlying the existing regulations in comparison to TSCA, and the fact that there are exceptions to the regulations EPA relies on to exclude these uses, indicate that any health and environmental risks resulting from still-allowed releases, including through the regulations' exceptions, may not have been addressed. EPA must include these uses in its risk evaluation and assess the risks associated with the remaining releases allowed under the regulations it cites.

Additionally, EPA's initial review of carbon tetrachloride uses identified a number of products with "commercial" uses that are available online that contained carbon tetrachloride.[124] EPA acknowledged that the sale of products containing carbon tetrachloride was foreseeable.[125] The table listed everything from carpet spot removers and adhesives, to pool paint, sealants, and drums of carbon tetrachloride available for purchase online.[126] EPA has not provided evidence refuting these uses of carbon tetrachloride,[127] and hence must address these products in the risk evaluation, since their availability online suggests there may be more than de minimis exposure to carbon tetrachloride in some consumer products.

C. EPA excludes all exposures to the general population while simultaneously stating that exposures to the general population are known or reasonably foreseeable.

EPA will exclude all exposures of carbon tetrachloride to the general population from the scope of the risk evaluation. (p. 56) This decision was made despite the fact that EPA indicates in numerous places in the problem formulation that the general population may well have exposures to carbon tetrachloride. For instance:

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[122] The Montreal Protocol on Substances that Deplete the Ozone Layer, 27th Meeting of the Parties (Nov. 2015), Decision XXVII/7: Investigation of carbon tetrachloride discrepancies, http://ozone.unep.org/node/94211.

[123] *Id.*

[124] U.S. EPA, *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Carbon Tetrachloride* at 15 (Feb. 2017), https://www.epa.gov/sites/production/files/2017-02/documents/carbon_tetrachloride.pdf.

[125] *Id.*

[126] *Id.* at 12.

[127] The Problem Formulation does include "[m]anufacturing of chlorinated compounds used in adhesives and sealants" and paints and coatings, (p. 25), but only as a commercial use.

1. When carbon tetrachloride is released as a result of industrial or commercial uses through the air or during disposal, inhalation is a "likely exposure pathway." (p. 37)
2. People can have inhalation exposures to carbon tetrachloride vapors in the shower and while dishwashing from contaminated water. (p. 37)
3. People can have inhalation exposure from vapor intrusion into indoor environments. (p. 38)
4. People may ingest contaminated drinking water or breast milk. (p. 38)
5. People may incidentally ingest carbon tetrachloride because of presence in water used for bathing or recreation. (p. 38)

Additionally, the National Institutes of Health's Report on Carcinogens states that EPA has estimated that "8 million people living within 12.5 miles of manufacturing sites were possibly exposed to carbon tetrachloride at an average concentration of 0.5 $\mu g/m^3$ and a peak concentration of 1,580 $\mu g/m^3$."[128] Despite EPA's identification of a number of exposures to the general population that are known or certainly reasonably foreseen, EPA has simply chosen to disregard all of these exposures. EPA's assertion that other statutes adequately address these exposures (without any analysis demonstrating that this is so), while simultaneously acknowledging that those exposures continue to happen, is arbitrary and capricious. *See State Farm*, 463 U.S. at 43 (an agency decision is arbitrary and capricious when it "entirely fail[s] to consider an important aspect of the problem").

EPA must analyze these known and reasonably foreseeable exposures to the general population to produce a risk evaluation consistent with reasonably available information and best available science.

D. There are a number of major deficiencies with other exclusions EPA includes in the carbon tetrachloride problem formulation.

Beyond the categorical exclusions that EPA has specifically identified (statutory, de minimis, etc.), which are addressed above, there are a number of other exclusions that EPA has made in the problem formulation for carbon tetrachloride without sufficient explanation or justification.

EPA will not consider exposures to a known decomposition product of carbon tetrachloride, phosgene. (p. 37) Phosgene exposures will be excluded because TRI data do not show releases of carbon tetrachloride and phosgene at the same facility. While that may be the case, there is at least one facility that reported releases of carbon tetrachloride under the National Emissions Inventory (NEI) and also reported data about phosgene emissions under the NEI and phosgene manufacture under the CDR.[129]

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[128] U.S. National Toxicology Program, *Report on Carcinogens: Carbon Tetrachloride* at 2 (14th ed. 2016), https://ntp.niehs.nih.gov/ntp/roc/content/profiles/carbontetrachloride.pdf.

[129] The 2014 NEI data states that 107 pounds of carbon tetrachloride were released from Sabic Innovative Plastics in Alabama, and that phosgene was also released from this facility. The 2016 CDR data for the same facility includes phosgene manufacture and states that "at least 100 but fewer than 500 workers" will likely be exposed to phosgene. While these data provide an incomplete picture of phosgene and carbon tetrachloride's dual presence at this facility, they indicate that EPA may have erred by relying solely on the TRI data.

EPA cannot rationally exclude this exposure by relying solely on TRI data because EPA must consider other reasonably available information. There are a number of other sources of data that are not as restrictive in scope as the TRI data, such as the NEI, that should be considered before excluding a potential exposure.[130] While EPA tries to support its exclusion by also stating that the decomposition of carbon tetrachloride is "more likely" to occur in open systems, which will allegedly not happen because EPA asserts carbon tetrachloride is only manufactured and processed in closed systems, EPA cites no sources to demonstrate that this is the case, nor does it explain how releases to the environment of carbon tetrachloride would not decompose and result in exposures to phosgene. EPA must consider carbon tetrachloride's decomposition into phosgene and any resulting exposures to phosgene.

Additionally, while not an explicitly addressed exclusion, there is no mention in the problem formulation of the potential for carbon tetrachloride to remain in the environment long after production and active use. Disregarding this is particularly problematic for carbon tetrachloride because EPA states that "[t]hough *** use has significantly decreased from a peak in the 1970's, its long half-life and previous ubiquitous use and disposal has resulted in [its] *continued presence* in various environmental media." (p. 34, emphasis added) Additionally, EPA noted that of eight HAPs monitored, "only carbon tetrachloride average concentrations have slightly increased in the atmosphere over the year period from 2003 to 2013." (p. 34) EPA does not attempt to address why there has been an increase in carbon tetrachloride concentrations in the air, nor whether or how it will address the continued presence of carbon tetrachloride in the environment.

In addition, EPA failed to acknowledge that there are Superfund sites all over the country with carbon tetrachloride contamination.[131] EPA's disregard of these sites is particularly egregious because EPA acknowledged that exposures to carbon tetrachloride persist despite its decreasing use, but then did not even attempt to offer an explanation as to why those exposures have been excluded. By remaining entirely silent on the potential exposures to carbon tetrachloride from Superfund sites, EPA's problem formulation is arbitrary and capricious. *See Ctr. for Biological Diversity v. United States BLM*, 698 F.3d 1101, 1124 (9th Cir. 2012) (concluding that it was arbitrary and capricious to entirely ignore the potential impact of groundwater withdrawals to a listed species).

E. EPA decided to "not further analyze" a number of pathways on cursory and unpersuasive grounds.

Aquatic Organisms: EPA plans to not further analyze pathways of exposure to ecological aquatic species, in part, because it asserts any carbon tetrachloride released to water will volatilize or dilute in surface water. (p. 48) EPA also states that:

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[130] *See* U.S. EPA, *Factors to Consider When Using Toxics Release Inventory Data* at 10 (2015), https://www.epa.gov/sites/production/files/2015-06/documents/factors_to_consider_6.15.15_final.pdf.

[131] Toxmap, which is provided by the National Institute of Health, indicates that there are 240 sites on the Superfund list that contain carbon tetrachloride as a pollutant. *See* https://toxmap.nlm.nih.gov/toxmap/app/; Appendix B at 7.

> EPA considered worst-case scenarios to estimate carbon tetrachloride concentrations in surface water resulting from industrial discharges. Using NPDES Discharge Monitoring Reporting data available for 2015, the largest releases of carbon tetrachloride were modeled for releases over 20 days and 250 days per year. In these *conservative* scenarios, surface water concentrations were below the acute COC [concentration of concern] for aquatic species (see Appendix E); hence there is not an acute aquatic concern. Although the chronic COC was exceeded by one facility by a factor of 3.5 (i.e., worst-case scenario) based on predicted *conservative* exposure concentrations in surface water, these carbon tetrachloride releases are not continuously released over time (i.e., chronic exposure); hence there is not a chronic aquatic concern. (p. 47, emphases added).

There are a number of concerns with EPA's assumptions here.

1. EPA says it has relied on NPDES data from 2015, and specifically included those data in its table in Appendix E. (p. 90) Yet that table does not include releases from one particular facility in 2015, a facility that released far more – 880 pounds – of carbon tetrachloride in one year than the facilities EPA included in its table, as seen below in the screenshot of EPA's ECHO database.[132] EPA does not explain why the discharges from this facility were not considered. Notably, this facility was not in violation of its NPDES permit, so there is no reason to believe it is an outlier.

Top Facility Discharges (2015)

NPDES ID	Facility Name	City, State	Report	SIC Code	HUC-12 Code	Avg Conc (mg/L)	Max Conc (mg/L)	Total Pounds (lb/yr)	Total TWPE (lb-eq/yr)	Avg Flow (MGD)
GA0003735	PINOVA, INC.	BRUNSWICK, GA	LE QP	2861	030702030203	0.0474	0.5000	880	299	9.35

2. In evaluating whether there is a concern for acute exposure, EPA only considered a 20-day release scenario, not shorter (even a single-day) release scenarios. The only reason EPA provides for this decision is that it is "not a likely scenario that would be allowed under current NPDES permit requirements." (p. 90) EPA provides no support for this statement. In fact, the NPDES permits for the two highest-releasing facilities in 2015 appear to have no concentration limits on carbon tetrachloride in their NPDES permits, only monitoring requirements.[133]
3. EPA states that there is no chronic concern because carbon tetrachloride is "not "continuously released over time." It is not clear how EPA could have reached this conclusion. The facilities EPA shows as having exceeded the chronic COC by a factor of 3.5 (the first row listed in Table

[132] *See* POLLUTANT LOADING REPORT, https://echo.epa.gov/trends/loading-tool/reports/dmr-pollutant-loading?permit_id=GA0003735&year=2015 (last visited Aug. 6, 2018).
[133] *See* NPDES for Pinova, Inc. in 2015, https://echo.epa.gov/trends/loading-tool/reports/permit-limits?permit_id=GA0003735&year=2015; NPDES for Fort Bend County WCID 2 in 2015, https://echo.epa.gov/trends/loading-tool/reports/permit-limits?permit_id=TX0021458&year=2015.

App. E-1 on p. 90) are POTWs [publicly owned treatment works] that discharge 365 days per year, according to EPA's own footnote to that table.

4. EPA dismisses exceedances of its chronic COC by claiming that "surface water concentrations that slightly exceed the chronic COC are not considered statistically significant as to present a concern for aquatic organisms." (p. 90) This raises the question why EPA bothered to do the analysis in the first place, if it then not only rejects the results, but then uses a cursory analysis and hand-waving arguments as a basis for its decision to do no further analysis at all of potential risks to aquatic organisms.
5. After asserting its analysis is conservative because it relied on "worst-case scenarios," EPA then dismisses exceedances revealed by its analysis by pulling back its claimed conservative assumptions. It cannot continue to claim its analysis is conservative.
6. Even using the 20-day scenario, EPA still found that "carbon tetrachloride surface water concentrations were mostly below the COCs for aquatic species," indicating that there were still some scenarios where the COC was exceeded. (p. 90, emphasis added) Indeed, several are shown in Table Apx E-1. EPA cannot ignore those scenarios especially because it cannot rule out that the discharges may have occurred over an even shorter time period than 20 days, which would have led to more exceedances.

Thus, EPA's analysis appears to be irrational and fails to establish that carbon tetrachloride will present no risks to aquatic organisms. EPA should prepare an accurate and logical analysis of the risks to aquatic species.

Sediment and Terrestrial Organisms: Despite the lack of *any* acceptable hazard studies for either group of organisms, EPA fails to require the development of any such hazard information, and also plans to exclude (or not further analyze, it is not exactly clear which) exposures to carbon tetrachloride for sediment and terrestrial organisms because it claims exposure is "not likely" due to carbon tetrachloride's fate and transport properties. (p. 39) EPA provides no analysis to support this assertion regarding exposure, and the lack of any hazard data raises the question as to what levels of exposure would present risk.

Yet among those fate and transport properties EPA invokes is volatility. Because carbon tetrachloride volatilizes from water, terrestrial organisms may be exposed to carbon tetrachloride through inhalation. Among the chemical's other properties are "its log Koc (1.7 – 2.16) and high solubility of 793 mg/L at 25°C," which EPA uses to argue that "sorption of carbon tetrachloride to sediments and suspended solids is unlikely." (p. 47) Yet those properties also mean the chemical will more likely be present in surface waters. EPA should analyze the air and water exposures faced by terrestrial organisms given that EPA's own analysis reveals that exposure is reasonably foreseen: "Terrestrial species populations living near industrial and commercial facilities using carbon tetrachloride may be exposed via multiple routes such as *ingestion of surface waters and inhalation of outdoor air*." (pp. 35-36) (emphasis added) EPA should also use its information authorities to obtain actual hazard information.

Occupational Non-users: EPA will also not analyze nearly all exposures of occupational non-users (ONU) to carbon tetrachloride for the majority of the release exposure scenarios for the industrial/commercial

uses of carbon tetrachloride. (pp. 92-103) Specifically, EPA is excluding all but one potential dermal exposure because ONU "would not intentionally handle liquids containing carbon tetrachloride," and because only workers will be "primarily" exposed. (pp. 93-103) TSCA provides no basis for limiting EPA's risk consideration only to intentional exposures, nor to focus only on persons "primarily" exposed. Additionally, EPA has simply assumed without analysis that the potential for occupational exposures to vapors to workers and ONU "may be low" in most scenarios. (pp. 92-95) Despite these assertions, the Occupational Safety and Health Administration (OSHA) has estimated that "3.4 million workers [were] potentially [ ] exposed to carbon tetrachloride directly or *indirectly*."[134] Given this estimate, EPA must actually analyze the exposures for workers and ONU.

Also, EPA was unable "to identify occupational exposure scenarios that correspond to several conditions of use due to a lack of understanding of those conditions of use." (p. 55) Although EPA appears to be taking steps to address these gaps, EPA must clarify that the exposure scenarios that remain unclear at this stage will receive further analysis in the risk evaluation. EPA should also use its information authorities under TSCA §§ 4 and 8 to fill these information gaps.

F. EPA's basis for excluding non-occluded dermal exposures to workers lacks rationale and is inconsistent with its approach to including occluded dermal exposures.

EPA's plan to only look at occluded dermal exposures is without sufficient justification. (p. 44) Specifically, EPA states that:

> There is the potential for dermal exposures to carbon tetrachloride in *many* worker scenarios. These dermal exposures would be concurrent with inhalation exposures and the overall contribution of dermal exposure to the total exposure is expected to be small; however, there may be exceptions for occluded scenarios. *** EPA plans to further analyze dermal exposures for skin contact with liquids and vapors in occluded situations for workers.

(p. 44, emphasis added) That there is a smaller relative percentage of exposure to carbon tetrachloride from dermal versus inhalation exposure does not mean that the dermal exposure is irrelevant to evaluating carbon tetrachloride's risks in occupational settings. The contribution to overall carbon tetrachloride exposure from dermal absorption could still be significant. EPA should consider combined exposures to carbon tetrachloride via all pathways across all potential sources of exposure.

G. EPA must analyze exposures to carbon tetrachloride from organic and inorganic chemical manufacturing.

EPA has identified as a condition of use the use of carbon tetrachloride as a process agent in the manufacturing of organic and inorganic compounds. (p. 25) While EPA has not expressly indicated it will do no further analysis of this use, EPA states that carbon tetrachloride is expected to only be present

[134] U.S. National Toxicology Program, Report on Carcinogens: Carbon Tetrachloride at 2 (14th ed. 2016), https://ntp.niehs.nih.gov/ntp/roc/content/profiles/carbontetrachloride.pdf (emphasis added).

"as an impurity rather than serving a specific function." (p. 86) In some of the other problem formulations, *e.g.,* HBCD, EPA has excluded a condition of use if EPA decided the chemical was not intentionally present or being used to serve a specific function. This exclusion has no basis in the law, and regardless of the function, it is still a known or reasonably foreseen, even if not intended, use of the chemical. EPA must address this condition of use in the risk evaluation.

29. The carbon tetrachloride problem formulation fails to identify relevant potentially exposed or susceptible subpopulations.

EPA only identifies workers and ONU as "potentially exposed or susceptible subpopulations." (p. 38) Unlike other problem formulations for the first ten chemicals where "[o]ther groups of individuals within the general population who may experience greater exposures due to their proximity to conditions of use" are identified as "potentially exposed or susceptible subpopulations," EPA has inexplicably failed to include that category of people as potentially exposed subpopulations in this problem formulation. This omission is despite the fact that, for example, "[p]oint sources of carbon tetrachloride from industry and wind direction are responsible for localized increases in air concentration."[135]

Such subpopulations fall squarely within the statutory definition of potentially exposed and susceptible subpopulations as "a group of individuals within the general population identified by the Administrator who, due to *** greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance." 15 U.S.C. § 2602(12). EPA should expressly identify them.

EPA has also failed to identify individuals who live near sites contaminated with carbon tetrachloride (e.g., Superfund sites) as a potentially exposed or susceptible subpopulation. As stated previously, there are 240 Superfund sites where carbon tetrachloride was identified as a pollutant, and EPA must identify residents in these communities as potentially exposed or susceptible subpopulations.

Moreover, while EPA has identified certain "factors that might influence susceptibility to carbon tetrachloride" (p. 43), EPA has failed to identify specific relevant vulnerable subpopulations based on greater susceptibility.

TSCA requires that EPA identify "potentially exposed or susceptible subpopulations" (TSCA section 6(b)(4)(D)), including those that "due to *** greater *susceptibility* *** may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture." 15 U.S.C. § 2602(12).

As described in Section 11.A of these comments, evidence before the agency shows that carbon tetrachloride presents potential developmental and reproductive risks, and hence infants, children, pregnant women, and adults of child-bearing age "may be at greater risk than the general population of

[135] U.S. National Toxicology Program, Report on Carcinogens: Carbon Tetrachloride at 2 (14th ed. 2016), https://ntp.niehs.nih.gov/ntp/roc/content/profiles/carbontetrachloride.pdf.

adverse health effects," and EPA must identify them as potentially exposed or susceptible subpopulations.

Carbon Tetrachloride Supplement:

2014 NEI Data for Carbon Tetrachloride	
Sector	**Emissions (LB)**
Industrial Processes - Chemical Manufacturing	89,839
Industrial Processes - Pulp & Paper	43,131
Waste Disposal	17,607
Fuel Comb - Industrial Boilers, ICEs - Biomass	12,131
Industrial Processes - Oil & Gas Production	12,050
Industrial Processes - Storage and Transfer	10,935
Industrial Processes – NEC	5,522
Fuel Comb - Electric Generation - Biomass	4,842
Fuel Comb - Industrial Boilers, ICEs - Natural Gas	3,076
Industrial Processes - Petroleum Refineries	1,169
Solvent - Industrial Surface Coating & Solvent Use	924
Fuel Comb - Electric Generation - Coal	599
Industrial Processes - Non-ferrous Metals	545
Fuel Comb - Comm/Institutional - Biomass	514
Industrial Processes - Cement Manufacturing	215
Fuel Comb - Comm/Institutional - Natural Gas	190
Industrial Processes - Ferrous Metals	130
Fuel Comb - Industrial Boilers, ICEs - Coal	103
Fuel Comb - Industrial Boilers, ICEs - Other	96

Fuel Comb - Electric Generation - Other	89
Solvent – Degreasing	54
Fuel Comb - Electric Generation - Natural Gas	42
Fuel Comb - Comm/Institutional - Other	40
Fuel Comb - Industrial Boilers, ICEs - Oil	32
Fuel Comb - Electric Generation - Oil	9
Fuel Comb - Comm/Institutional - Oil	4
Solvent - Consumer & Commercial Solvent Use	1